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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT

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                MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
                AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
NEWS HOURS      STN Operating Hours Plus Help Desk Availability
NEWS INTER      General Internet Information
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NEWS PHONE      Direct Dial and Telecommunication Network Access to STN
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                                                      ENTRY     SESSION
FULL ESTIMATED COST                                    0.21        0.21

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CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 10:51:49 ON 04 JUN 2003
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=> s (MHC class II transactivator) or (type II bare lymphocyte syndrome()associated
factor) or mhc2ta or ciita or c2ta or (mchii transactivator)
L1         1598 (MHC CLASS II TRANSACTIVATOR) OR (TYPE II BARE LYMPHOCYTE SYNDRO
                ME(W) ASSOCIATED FACTOR) OR MHC2TA OR CIITA OR C2TA OR (MCHII
                TRANSACTIVATOR)

=> s l1 and (antisens? or triplex or ribozym? or RNAi or (rna interference) or
sirna or ptgs or quelling)
L2           54 L1 AND (ANTISENS? OR TRIPLEX OR RIBOZYM? OR RNAI OR (RNA INTERFE
                RENCE) OR SIRNA OR PTGS OR QUELLING)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3           47 DUP REM L2 (7 DUPLICATES REMOVED)

=> d l3 ibib abs tot

L3   ANSWER 1 OF 47  USPATFULL
ACCESSION NUMBER:       2003:127207  USPATFULL
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TITLE: Transgenic animals and cells expressing proteins necessary for susceptibility to HIV infection

INVENTOR(S): Yoshiki, Takashi, Hokkaido, JAPAN
Lai, Yorong, Hokkaido, JAPAN
Ikeda, Hitoshi, Hokkaido, JAPAN

PATENT ASSIGNEE(S): GeneticLab Co., Ltd., Hokkaido, JAPAN (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003087420	A1	20030508
APPLICATION INFO.:	US 2002-176966	A1	20020621 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2001-191416	20010625

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY & LARDNER, P.O. Box 80278, San Diego, CA, 92138-0278
NUMBER OF CLAIMS: 60
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides mammalian cells and mammalian animals that produce HIV particles. The rodent animals of the present invention are able to stably express a human CD4, a human chemokine receptor (such as CXCR4 or CCR5), a human cyclin T1, and a human class II transactivator (**CIITA**), and produce HIV virus particles. Also provided are methods of preparing the transgenic cells and rodent animals of the invention, as well as methods of using them to identify and assay test agents for anti-HIV activity. Also provided are methods and pharmaceutical compositions for treating and preventing HIV infection in a mammal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 2 OF 47 USPATFULL
ACCESSION NUMBER: 2003:127128 USPATFULL
TITLE: 49 human secreted proteins

INVENTOR(S): Moore, Paul A., Germantown, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Olsen, Henrik S., Gaithersburg, MD, UNITED STATES
Shi, Yanggu, Gaithersburg, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Florence, Kimberly A., Rockville, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
LaFleur, David W., Washington, DC, UNITED STATES
Endress, Gregory A., Potomac, MD, UNITED STATES
Ebner, Reinhard, Gaithersburg, MD, UNITED STATES
Komatsoulis, George, Silver Spring, MD, UNITED STATES
Duan, Roxanne D., Bethesda, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003087341	A1	20030508
APPLICATION INFO.:	US 2002-54988	A1	20020125 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-904615, filed on 16 Jul 2001, PENDING Continuation of Ser. No. US 2000-739254, filed on 19 Dec 2000, ABANDONED Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-97917P	19980825 (60)
	US 1998-98634P	19980831 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 19398
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 3 OF 47 USPATFULL
ACCESSION NUMBER: 2003:100088 USPATFULL
TITLE: Treatment methods based on microcompetition for a limiting GABP complex
INVENTOR(S): Polansky, Hanan, Rochester, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003069199	A1	20030410
APPLICATION INFO.:	US 2002-219334	A1	20020815 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-732360, filed on 7 Dec 2000, PENDING

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Hanan Polansky, 3159 S. Winton Rd., Rochester, NY, 14623

NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 28 Drawing Page(s)
LINE COUNT: 14837
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Microcompetition for GABP between a foreign polynucleotide and a cellular GABP regulated gene is a risk factor associated with chronic disease such as obesity, cancer, atherosclerosis, stroke, osteoarthritis, diabetes, asthma, and other autoimmune diseases. The invention uses this novel discovery to present methods for the treatment of these chronic diseases. The methods are based on modifying such microcompetition, or the effect of such microcompetition on the cell. For instance, treatment may modify the cellular copy number of the foreign polynucleotide, change the rate of complex formation between GABP and either the foreign polynucleotide or the cellular GABP regulated gene, vary the expression of the cellular GABP regulated gene, or manipulate the activity of the gene product of the cellular GABP regulated gene. The invention also presents methods for treatment of chronic diseases resulting from other foreign polynucleotide-type disruptions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 4 OF 47 USPATFULL
ACCESSION NUMBER: 2003:99511 USPATFULL
TITLE: Drug discovery assays based on microcompetition for a limiting GABP complex

INVENTOR(S): Polansky, Hanan, Rochester, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003068616	A1	20030410
APPLICATION INFO.:	US 2002-223050	A1	20020814 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-732360, filed on 7 Dec 2000, PENDING

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Hanan Polansky, 3159 S. Winton Rd., Rochester, NY, 14623
NUMBER OF CLAIMS: 55
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 28 Drawing Page(s)
LINE COUNT: 14981
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A recent discovery showed that microcompetition for GABP between a foreign polynucleotide and a cellular GABP regulated gene is a risk factor for some of the major chronic diseases, such as obesity, cancer, atherosclerosis, stroke, osteoarthritis, diabetes, asthma, and other autoimmune diseases. The invention uses this novel discovery to present assays for screening compounds based on their effectiveness in modulating such microcompetition, or the effects of such microcompetition on the cell. The selected compounds can be used in treatment of these chronic diseases. The invention also presents assays for screening compounds that can be used in treatment of chronic diseases resulting from other foreign polynucleotide-type disruptions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 5 OF 47 USPATFULL
ACCESSION NUMBER: 2003:78472 USPATFULL
TITLE: Design principle for the construction of expression constructs for gene therapy
INVENTOR(S): Wittig, Burghardt, Berlin, GERMANY, FEDERAL REPUBLIC OF
Junghans, Claas, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): SOFT GENE GMBH (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003054392	A1	20030320
APPLICATION INFO.:	US 2002-228811	A1	20020827 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-310842, filed on 12 May 1999, GRANTED, Pat. No. US 6451593

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1996-19648625	19961113

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: NILS H. LJUNGMAN, NILS H. LJUNGMAN & ASSOCIATES, P.O. BOX 130, GREENSBURG, PA, 15601-0130
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 879
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns an expressible nucleic acid construct, which contains only the sequence information necessary for expressing a gene for RNA or protein synthesis. Expression constructs of this type can be used in gene therapy and genetic vaccination and avoid many of the risks associated with constructs today. The invention further concerns the possibility of improving the conveying of the construct into cells or tissue by covalent linkage of the construct, for example to particles of

peptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 6 OF 47 USPATFULL

ACCESSION NUMBER:	2003:78445 USPATFULL
TITLE:	MHC class II antigen presenting cells containing oligonucleotides which inhibit Ii protein expression
INVENTOR(S):	Xu, Minzhen, Northborough, MA, UNITED STATES Qiu, Gang, Shewsbury, MA, UNITED STATES Humphreys, Robert, Acton, MA, UNITED STATES
PATENT ASSIGNEE(S):	Antigen Express, Inc., Worcester, MA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003054365	A1	20030320
APPLICATION INFO.:	US 2002-54387	A1	20020122 (10)

RELATED APPLN. INFO.:	Division of Ser. No. US 1998-205995, filed on 4 Dec 1998, GRANTED, Pat. No. US 6368855 Continuation-in-part of Ser. No. US 1998-36746, filed on 9 Mar 1998, ABANDONED Continuation of Ser. No. US 1996-661627, filed on 11 Jun 1996, GRANTED, Pat. No. US 5726020
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Kevin M. Farrell, Kevin M. Farrell, P.C., 18 York Street, P.O. Box 999, York Harbor, ME, 03911
NUMBER OF CLAIMS:	96
EXEMPLARY CLAIM:	1
LINE COUNT:	3050

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a specific regulator of Ii protein expression or immunoregulatory function. Specifically disclosed are several forms of the specific regulator of Ii, including those which function through the formation of a duplex molecule with an RNA molecule encoding mammalian Ii protein to inhibit Ii protein synthesis at the translation level. This class includes copolymers comprised of nucleotide bases which hybridize specifically to the RNA molecule encoding mammalian Ii protein, and also expressible reverse gene constructs. In other aspects, the disclosure relates to MHC class II-positive antigen presenting cells containing a specific regulator of Ii expression. Such cells are useful, for example, in the display of autodeterminant peptides in association with MHC class II proteins. Compositions of the invention find application in methods for treating diseases, for example malignancies and autoimmune disorders, in a patient by enhancing immunological attack on undesired cells. An additional application is the isolation of autodeterminant peptides from a cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 7 OF 47 USPATFULL

ACCESSION NUMBER:	2003:70969 USPATFULL
TITLE:	Modulating neuronal outgrowth via the major histocompatibility complex Class I (MHC I) molecule
INVENTOR(S):	Kaufman, Daniel L., Los Angeles, CA, UNITED STATES Hanssen, Lorraine, Los Angeles, CA, UNITED STATES Zekzer, Dan, Encinitas, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003049254	A1	20030313
APPLICATION INFO.:	US 2002-161647	A1	20020605 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-295596P	20010605 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Sharon E. Crane, Ph.D., BURNS, DOANE, SWECKER & MATHIS, L.L.P., P.O. Box 1404, Alexandria, VA, 22313-1404
NUMBER OF CLAIMS: 66
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 2511
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to methods and compositions for treating neural damage caused by injury or disease, by enhancing neural outgrowth and/or repair responses in the nervous system. Preferably, the methods and compositions utilize agents which interfere with the ability of the major histocompatibility complex (MHC) Class I molecule (MHC I) to inhibit neurite outgrowth. Such agents include antibodies directed to MHC I, MHC I fragments and/or analogs, and agents which interfere with MHC I interaction with its neuronal receptor and the receptor's signaling pathway.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 8 OF 47 USPATFULL
ACCESSION NUMBER: 2003:44848 USPATFULL
TITLE: Method of modulating the efficiency of translation termination and degradation of aberrant mRNA involving a surveillance complex comprising human Upf1p,eucaryotic release factor 1 and eucaryotic release factor 3
INVENTOR(S): Peltz, Stuart, Piscataway, NJ, UNITED STATES
Czaplinski, Kevin, Somerset, NJ, UNITED STATES
Weng, Youmin, Cranford, NJ, UNITED STATES
PATENT ASSIGNEE(S): University of Medicine and Dentistry of New Jersey, New Brunswick, NY, UNITED STATES, 08903 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003032158	A1	20030213
APPLICATION INFO.:	US 2002-138784	A1	20020503 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-321649, filed on 28 May 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-86986P	19980528 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PERKINS COIE LLP, POST OFFICE BOX 1208, SEATTLE, WA, 98111-1208
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 2935
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided are novel methods and assays to identify agents and compositions that modulate the ability of the eukaryotic surveillance complex to effect translation termination and degradation of aberrant mRNA.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 9 OF 47 USPATFULL
ACCESSION NUMBER: 2003:44371 USPATFULL
TITLE: Combined growth factor-deleted and thymidine kinase-deleted vaccinia virus vector
INVENTOR(S): McCart, J. Andrea, Toronto, CANADA

Bartlett, David L., Pittsburgh, PA, UNITED STATES
Moss, Bernard, Bethesda, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003031681	A1	20030213	
APPLICATION INFO.:	US 2001-991721	A1	20011113	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	WO 2000-US14679	20000526	
	US 1999-137126P	19990528	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KNOBBE MARTENS OLSON & BEAR LLP, 2040 MAIN STREET, FOURTEENTH FLOOR, IRVINE, CA, 91614

NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 2762
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A composition of matter comprising a vaccinia virus expression vector with a negative thymidine kinase phenotype and a negative vaccinia virus growth factor phenotype.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 10 OF 47 USPATFULL
ACCESSION NUMBER: 2003:74268 USPATFULL
TITLE: Method for identifying a compound to be tested for an ability to reduce immune rejection by determining Stat4 and Stat6 proteins
INVENTOR(S): Hancock, Wayne William, Medfield, MA, United States
Ozkaynak, Engin, Milford, MA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6534277	B1	20030318	
APPLICATION INFO.:	US 2001-972800		20011005	(9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2000-549654, filed on 14 Apr 2000, now abandoned			

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Kemmerer, Elizabeth
ASSISTANT EXAMINER: Li, Ruixiang
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 69 Drawing Figure(s); 64 Drawing Page(s)
LINE COUNT: 7647
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods for identifying compounds that can reduce immune rejection, for example, transplant- or autoimmune disorder-related immune rejection. The present invention is based, in part, on the discovery, demonstrated herein, that immune rejection can be monitored by determining the amount of particular members of the Jak/Stat signal transduction pathway present within an affected tissue. The present invention is further based, in part, on the discovery, demonstrated herein, that immune rejection can be reduced and tolerance can be induced by modulating the amount of these particular members of the Jak/Stat signal transduction pathway present, expressed or active within an affected tissue. In particular, the results demonstrate that immune rejection can be monitored by determining the amount of mRNA or

protein of Stat1, Stat3, Stat4, Stat6, SOCS1, or SOCS3 present, e.g., in an affected tissue.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 11 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:388421 CAPLUS
TITLE: Radiation Improves Intratumoral Gene Therapy for Induction of Cancer Vaccine in Murine Prostate Carcinoma
AUTHOR(S): Hillman, Gilda G.; Xu, Minzhen; Wang, Yu; Wright, Jennifer L.; Lu, Xueqing; Kallinteris, Nikoletta L.; Tekyi-Mensah, Samuel; Thompson, Timothy C.; Mitchell, Malcolm S.; Forman, Jeffrey D.
CORPORATE SOURCE: Department of Radiation Oncology, Barbara Ann Karmanos Cancer Institute at Wayne State University School of Medicine and Harper Hospital, Detroit, MI, 48201, USA
SOURCE: Human Gene Therapy (2003), 14(8), 763-775
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our goal was to convert murine RM-9 prostate carcinoma cells in vivo into antigen-presenting cells capable of presenting endogenous tumor antigens and triggering a potent T-helper cell-mediated immune response essential for the generation of a specific antitumor response. We showed that generating the major histocompatibility complex (MHC) class I+/class II+/Ii- phenotype, within an established s.c. RM-9 tumor nodule, led to an effective immune response limiting tumor growth. This phenotype was created by intratumoral injection of plasmid cDNAs coding for interferon gamma, **MHC class II transactivator**, and an **antisense** reverse gene construct (RGC) for a segment of the gene for Ii protein (-92,97). While this protocol led to significant suppression of tumor growth, there were no disease-free survivors. Nevertheless, irradn. of the tumor nodule on the day preceding initiation of gene therapy yielded 7 of 16 mice that were disease-free in a long-term follow up of 57 days compared to 1 of 7 mice receiving radiotherapy alone. Mice receiving radiotherapy and gene therapy rejected challenge with parental RM-9 cells and demonstrated specific cytotoxic T-cell activity in their splenocytes but not the mouse cured by radiation alone. These data were reproduced in addnl. expts. and confirmed that tumor irradn. prior to gene therapy resulted in complete tumor regression and specific tumor immunity in more than 50% of the mice. Increasing the no. of plasmid injections after tumor irradn. induced tumor regression in 70% of the mice. Administering radiation before this novel gene therapy approach, that creates an in situ tumor vaccine, holds promise for the treatment of human prostate carcinoma.

L3 ANSWER 12 OF 47 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:271955 CAPLUS
DOCUMENT NUMBER: 136:308521
TITLE: **Antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression
INVENTOR(S): Xu, Minzhen; Qiu, Gang; Humphreys, Robert
PATENT ASSIGNEE(S): Antigen Express, Inc., USA
SOURCE: U.S., 36 pp., Cont.-in-part of U.S. Ser. No. 36,746, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 6368855	B1	20020409	US 1998-205995	19981204
US 5726020	A	19980310	US 1996-661627	19960611
WO 2000034467	A1	20000615	WO 1999-US28096	19991124
W: AU, CA, CN, JP, KR				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1135482	A1	20010926	EP 1999-961831	19991124
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002531582	T2	20020924	JP 2000-586901	19991124
US 2003054365	A1	20030320	US 2002-54387	20020122

PRIORITY APPLN. INFO.:
US 1996-661627 A1 19960611
US 1998-36746 B2 19980309
US 1998-205995 A 19981204
WO 1999-US28096 W 19991124

AB Disclosed is a specific regulator of Ii protein (class II antigen invariant chain) gene expression or immunoregulatory function. Specifically disclosed are several forms of the specific regulator of Ii, including those which function through the formation of a duplex mol. with an RNA mol. encoding mammalian Ii protein to inhibit Ii protein synthesis at the translation level. This class includes copolymers comprised of nucleotide bases which hybridize specifically to the RNA mol. encoding mammalian Ii protein, and also expressible reverse gene constructs. In other aspects, the disclosure relates to MHC class II-pos. antigen presenting cells contg. a specific regulator of Ii expression. Such cells are useful, for example, in the display of autodeterminant peptides in assocn. with MHC class II proteins. Compns. of the invention find application in methods for treating diseases, for example malignancies and autoimmune disorders, in a patient by enhancing immunol. attack on undesired cells. An addnl. application is the isolation of autodeterminant peptides from a cell. RNAse H mapping was used to identify sites on the Ii mRNA that are accessible to **antisense** oligonucleotides. Use of phosphorothioate oligonucleotides is demonstrated in vitro. The most effective of the **antisense** oligonucleotides was used to inhibit Ii gene expression in the sarcoma cell line SaI in which MHCII antigen gene expressed was increased by overexpression of the **CIITA** gene. Formaldehyde fixed Ii-deficient cells were used to inoculate mice. Mice challenged with 20.times.105 SaI cells did not develop tumors.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 47 USPATFULL

ACCESSION NUMBER: 2002:294261 USPATFULL
TITLE: TNF and IFN stimulated genes and uses therefor
INVENTOR(S): Wong, Grace, Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164299	A1	20021107
APPLICATION INFO.:	US 2001-854432	A1	20010511 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-203624P	20000512 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Dike, Bronstein, Roberts & Cushman, Intellectual Property Patent Practice, EDWARDS & ANGELL, LLP, 130 Water Street, Boston, MA, 02109
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
LINE COUNT: 1720
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to the identification of genes that are expressed at a higher level in certain TNF & IFN treated cells than in otherwise identical untreated cells. Genes that are expressed at a higher level in TNF & IFN treated cells than untreated cells ("TNF & IFN stimulated genes") are of interest, in part, because TNF & IFN can or could influence a wide range of cellular processes and responses for antiviral activity. The identified TNF & IFN stimulated genes and the proteins they encode can be used: 1) as therapeutic agents which modulate a cellular process or response that is influenced by TNF & IFN; 2) as targets for use in high throughput screening and the development of therapeutic agents which modulate a cellular process or response that is influenced by TNF & IFN; and 3) as markers which can be used to detect and monitor a cellular process or response that is influenced by TNF & IFN.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 14 OF 47 USPATFULL

ACCESSION NUMBER: 2002:280808 USPATFULL

TITLE: Transcription factor of MHC class II genes, substances capable of inhibiting this new transcription factor and medical uses of these substances

INVENTOR(S): Masternak, Krzysztof, Morges, SWITZERLAND
Reith, Walter, Carouge, SWITZERLAND
Mach, Bernard, Pregny-Chambesy, SWITZERLAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002156258	A1	20021024
APPLICATION INFO.:	US 2001-840243	A1	20010424 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 1999-EP8026, filed on 22 Oct 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	EP 1998-120085	19981024

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BURNS DOANE SWECKER & MATHIS L L P, POST OFFICE BOX 1404, ALEXANDRIA, VA, 22313-1404
NUMBER OF CLAIMS: 61
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 19 Drawing Page(s)
LINE COUNT: 2908
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel trancription factor of MHC class II genes and its derivatives, inhibitors down-regulating the expression of MHC class II molecules, process to identify these inhibitors and medical uses of these inhibitors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 15 OF 47 USPATFULL

ACCESSION NUMBER: 2002:273560 USPATFULL

TITLE: NUCLEIC ACID SEQUENCES OF **CIITA** GENES WHICH CAN BE INVOLVED IN CONTROLLING AND REGULATING THE EXPRESSION OF GENES ENCODING MHC TYPE II MOLECULES, AND THEIR USE, IN PARTICULAR AS DRUGS.

INVENTOR(S): MACH, BERNARD, GENEVA, SWITZERLAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002151691	A1	20021017
APPLICATION INFO.:	US 1998-64199	A1	19980422 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1997-4954	19970422

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BURNS DOANE SWECKER & MATHIS L L P, POST OFFICE BOX 1404, ALEXANDRIA, VA, 22313-1404

NUMBER OF CLAIMS: 59
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 2819
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to nucleic acid sequences which comprise all or part of a nucleic acid sequence of a **CIITA** gene. These sequences can comprise a sequence which exhibits a transcriptional promoter activity, which activity is, in particular, specifically expressed in one cell type. The sequences can also comprise a coding sequence.

Therapeutic and diagnostic applications, in particular relating to disorders in which it is desirable to act on the level at which genes which encode the class II molecules of the major histocompatibility complex (MHC) are expressed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 16 OF 47 USPATFULL
ACCESSION NUMBER: 2002:265930 USPATFULL
TITLE: **CIITA**-interacting proteins and methods of use therefor
INVENTOR(S): Glimcher, Laurie H., West Newton, MA, UNITED STATES
Zhou, Hong, Wilmington, DE, UNITED STATES
PATENT ASSIGNEE(S): President and Fellows of Harvard College (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002146806	A1	20021010
APPLICATION INFO.:	US 2002-121882	A1	20020412 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-965272, filed on 6 Nov 1997, GRANTED, Pat. No. US 6410261
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 2820
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated nucleic acid molecules encoding a novel protein, CIP104, that interacts with **CIITA**, an MHC class II transcriptional activator, are disclosed. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals carrying a CIP104 transgene. The invention further provides isolated CIP104 proteins and peptides, CIP104 fusion proteins and anti-CIP104 antibodies. Methods of using the CIP104 compositions of the invention are also disclosed, including methods for detecting CIP104 activity (e.g, CIP104 protein or mRNA) in a biological sample, methods of modulating CIP104 activity in a cell, and methods for identifying agents that modulate an interaction between CIP104 and **CIITA**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 17 OF 47 USPATFULL
ACCESSION NUMBER: 2002:259402 USPATFULL
TITLE: IMMUNE ACTIVATION BY DOUBLE-STRANDED POLYNUCLEOTIDES
INVENTOR(S): KOHN, LEONARD D., BETHESDA, MD, UNITED STATES
SUZUKI, KOICHI, NORTH BETHESDA, MD, UNITED STATES
MORI, ATSUMI, BETHESDA, MD, UNITED STATES
IISHI, KEN, ROCKVILLE, MD, UNITED STATES
KLINMAN, DENNIS M., POTOMAC, MD, UNITED STATES
RICE, JOHN M., WEST CHESTER, OH, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002142974	A1	20021003	
APPLICATION INFO.:	US 1998-151612	A1	19980911	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Steven J. Goldstein, FROST BROWN TODD LLC, 2200 PNC Center, 201 East Fifth Street, Cincinnati, OH, 45202
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Page(s)
LINE COUNT: 4436
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Double-stranded polynucleotide activates the expression of immune recognition molecules. The polynucleotide can have a minimal length and activates the expression of molecules not encoded by a nucleotide sequence that is not necessarily related to the polynucleotide. The present invention provides for a simple and specific system to activate expression of Class I and/or Class II molecules of the major histocompatibility complex (MHC), and allows regulation of expression of MHC molecules on the cell-surface of antigen presenting cells and other immune cells. Also provided are systems for the screening, identification, and isolation of compounds that increase or decrease this activation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 18 OF 47 USPATFULL
ACCESSION NUMBER: 2002:251947 USPATFULL
TITLE: Phospholipid Scramblases and methods of use thereof
INVENTOR(S): Sims, Peter J., Del Mar, CA, UNITED STATES
Wiedmer, Therese, Del Mar, CA, UNITED STATES
Silverman, Robert H., Beachwood, OH, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002137905	A1	20020926	
APPLICATION INFO.:	US 2001-823847	A1	20010330	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-193939P	20000331	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A. Haile, Ph.D., Gray Cary Ware & Freidenrich LLP, 4365 Executive Drive, Suite 1600, San Diego, CA, 92121-2189
NUMBER OF CLAIMS: 58
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 3514
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is based on a family of membrane proteins, Phospholipid Scramblases (PLSCR), that mediate accelerated trans-bilayer movement of plasma membrane phospholipids in response to elevated

cytoplasmic calcium. At least one Phospholipid Scramblase gene is highly inducible by interferon. Interferon-induced expression of Phospholipid Scramblase 1 (and/or related genes) alters the physical and functional properties of the cell surface so as to (1) inhibit tumor cell proliferation and survival; (2) inhibit maturation and release of membrane-enveloped viruses; and/or (3) promote clearance of virus-infected cells and cancer cells through the reticuloendothelial system. The present invention provides Phospholipid Scramblase polypeptides, polynucleotide sequences that encode Phospholipid Scramblase polypeptides, and antibodies that are immunoreactive with the polypeptides. The finding that human Phospholipid Scramblase 1 polypeptides are induced by interferons, indicates a role for the Scramblase polypeptides in treating and preventing cancer and viral infection.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 19 OF 47 USPATFULL

ACCESSION NUMBER: 2002:179280 USPATFULL
TITLE: Clinically intelligent diagnostic devices and mehtods
INVENTOR(S): Jacobs, Alice A., Boston, MA, UNITED STATES
Gupta, Vineet, Brookline, MA, UNITED STATES
Nikolic, Boris, Charlestown, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002095073	A1	20020718	
APPLICATION INFO.:	US 2001-996056	A1	20011127	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-253284P	20001127 (60)
	US 2001-287994P	20010501 (60)
	US 2001-308870P	20010730 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: J. PETER FASSE, Fish & Richardson P.C., 225 Franklin Street, Boston, MA, 02110-2804

NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 38 Drawing Page(s)
LINE COUNT: 2940

AB The invention relates to the clinically intelligent design of diagnostic devices (such as microarrays) and methods of making and using such devices in differential diagnoses of specific clinical symptoms or sets of symptoms. In one aspect, the devices include various probes used to perform parallel screening of a number of analytes. The probes are clustered on the devices based on known clinical presentations of symptoms associated with specific diseases and disorders.

L3 ANSWER 20 OF 47 USPATFULL

ACCESSION NUMBER: 2002:55155 USPATFULL
TITLE: Human single nucleotide polymorphisms
INVENTOR(S): Cargill, Michele, Gaithersburg, MD, UNITED STATES
Ireland, James S., Gaithersburg, MD, UNITED STATES
Lander, Eric S., Cambridge, MA, UNITED STATES

PATENT ASSIGNEE(S): Whitehead Institute for Biomedical Research, Cambridge, MA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002032319	A1	20020314	
APPLICATION INFO.:	US 2001-801274	A1	20010307	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-187510P	20000307 (60)
	US 2000-206129P	20000522 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON BROOK SMITH AND REYNOLDS, P.C., TWO MILITIA DR, LEXINGTON, MA, 02421-4799

NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 8981
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides nucleic acid segments of the human genome, particularly nucleic acid segments from genes including polymorphic sites. Allele-specific primers and probes hybridizing to regions flanking or containing these sites are also provided. The nucleic acids, primers and probes are used in applications such as phenotype correlations, forensics, paternity testing, medicine and genetic analysis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 21 OF 47 USPATFULL
ACCESSION NUMBER: 2002:48291 USPATFULL
TITLE: NIP45 HUMAN HOMOLOG
INVENTOR(S): ZHOU, HONG, WILMINGTON, DE, UNITED STATES
ZHOAO, JIUQIAO, HOCKESSIN, DE, UNITED STATES
LIU, DERONG, WILMINGTON, DE, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002028482	A1	20020307
APPLICATION INFO.:	US 1998-175254	A1	19981020 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1997-22388	19971024

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LIPD DEPT (FOC 1 S/E), ZENECA INC, 1800 CONCORD PIKE, P O BOX 5437, WILMINGTON, DE, 198505437

NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 2356
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A human NIP45 polypeptide is described which trans-activates transcription of the human IL-4 gene. A full length cDNA which encodes the novel trans-activator polypeptide is disclosed as well as the interior structural region and the amino acid residue sequence of the human NIP45. Methods are provided to identify compounds that modulate the biological activity of the native IL-4 transcription associated biomolecule and hence regulate IL-4 transcription.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 22 OF 47 USPATFULL
ACCESSION NUMBER: 2002:43671 USPATFULL
TITLE: 49 human secreted proteins
INVENTOR(S): Moore, Paul A., Germantown, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Olsen, Henrik S., Gaithersburg, MD, UNITED STATES
Shi, Yanggu, Gaithersburg, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Florence, Kimberly A., Rockville, MD, UNITED STATES

Soppet, Daniel R., Centreville, VA, UNITED STATES
LaFleur, David W., Washington, DC, UNITED STATES
Endress, Gregory A., Potomac, MD, UNITED STATES
Ebner, Reinhard, Gaithersburg, MD, UNITED STATES
Komatsoulis, George, Silver Spring, MD, UNITED STATES
Duan, Roxanne D., Bethesda, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002026040	A1	20020228
	US 6566325	B2	20030520
APPLICATION INFO.:	US 2001-904615	A1	20010716 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-739254, filed on 19 Dec 2000, PENDING Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-97917P	19980825 (60)
	US 1998-98634P	19980831 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 19401
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 23 OF 47 USPATFULL
ACCESSION NUMBER: 2002:32691 USPATFULL
TITLE: **CIITA**-INTERACTING PROTEINS AND METHODS OF USE THEREFOR
INVENTOR(S): GLIMCHER, LAURIE H., WEST NEWTON, MA, UNITED STATES
ZHOU, HONG, WILMINGTON, DE, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002019514	A1	20020214
	US 6410261	B2	20020625
APPLICATION INFO.:	US 1997-965272	A1	19971106 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CYNTHIA L. KANIK Ph.D, LAHIVE & COCKFIELD LLP, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 2821
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated nucleic acid molecules encoding a novel protein, CIP104, that interacts with **CIITA**, an MHC class II transcriptional activator, are disclosed. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors

containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals carrying a CIP104 transgene. The invention further provides isolated CIP104 proteins and peptides, CIP104 fusion proteins and anti-CIP104 antibodies. Methods of using the CIP104 compositions of the invention are also disclosed, including methods for detecting CIP104 activity (e.g., CIP104 protein or mRNA) in a biological sample, methods of modulating CIP104 activity in a cell, and methods for identifying agents that modulate an interaction between CIP104 and **CIITA**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 24 OF 47 USPATFULL

ACCESSION NUMBER:	2002:346979 USPATFULL
TITLE:	Composition for the detection of signaling pathway gene expression
INVENTOR(S):	Au-Young, Janice, Berkeley, CA, United States Seilhamer, Jeffrey J., Los Altos Hills, CA, United States
PATENT ASSIGNEE(S):	Incyte Genomics, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6500938	B1	20021231	
APPLICATION INFO.:	US 1998-16434		19980130	(9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Marschel, Ardin H.
LEGAL REPRESENTATIVE:	Incyte Genomics, Inc.
NUMBER OF CLAIMS:	5
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT:	6180

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a composition comprising a plurality of polynucleotide probes. The composition can be used as array elements in a microarray. The present invention also relates to a method for selecting polynucleotide probes of the composition.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 25 OF 47 USPATFULL

ACCESSION NUMBER:	2002:311029 USPATFULL
TITLE:	METHOD OF MODULATING THE EFFICIENCY OF TRANSLATION TERMINATION AND DEGRADATION OF ABERRANT MRNA INVOLVING A SURVEILLANCE COMPLEX COMPRISING HUMAN UPF1P, EUCARYOTIC RELEASE FACTOR 1 AND EUCARYOTIC RELEASE FACTOR 3
INVENTOR(S):	Peltz, Stuart, 67 Castle Pointe Blvd., Piscataway, NJ, United States 08854 Czaplinski, Kevin, 115 Hollywood Ave., Somerset, NJ, United States 08873 Weng, Youmin, 2 Indian Spring Rd., Cranford, NJ, United States 07016

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6486305	B1	20021126	
APPLICATION INFO.:	US 2000-639987		20000816	(9)

RELATED APPLN. INFO.:	Division of Ser. No. US 1998-86260, filed on 28 May 1998, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	McCarry, Sean

ASSISTANT EXAMINER: Zara, Jane
LEGAL REPRESENTATIVE: Lyon & Lyon LLP
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 2808
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method of modulating translation termination efficiency of mRNA and/or promoting degradation of abberant transcripts. Also, this invention provides a method of screening for a drug active involved in enhancing translation termination and a method for identifying a disease state involving defective the protein complex.

This invention provides a purified complex comprising an amount of a human Upf1p protein, a peptidyl eucaryotic release factor 1 (eRF1) and a peptidyl eucaryotic release factor 3 (eRF3) effective to modulate translation termination. Further, this invention provides an expression vector which comprises a nucleic acid encoding a human Upf1p protein, a peptidyl eucaryotic release factor 1 (eRF1) and a peptidyl eucaryotic release factor 3 (eRF3) operably linked to a regulatory element.

This invention provides an antibody which binds to the complex comprising an amount of a human Upf1p protein, a peptidyl eucaryotic release factor 1 (eRF1) and a peptidyl eucaryotic release factor 3 (eRF3) effective to modulate translation termination. This invention provides an agent which inhibits or modulates the binding of human Upf1p to eRF1 or eRF3 The agent may inhibit or facilitate the binding of human Upf1p to eRF1 or eRF3.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 26 OF 47 USPATFULL
ACCESSION NUMBER: 2002:238872 USPATFULL
TITLE: Design principle for construction of expression constructs for gene therapy
INVENTOR(S): Wittig, Burghardt, Berlin, GERMANY, FEDERAL REPUBLIC OF
Junghans, Claas, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): Soft Gene GmbH, Berlin, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6451593	B1	20020917
APPLICATION INFO.:	US 1999-310842		19990512 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 1997-DE2704, filed on 13 Nov 1997		

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1996-19648625	19961113

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Priebe, Scott D.
ASSISTANT EXAMINER: Kaushal, Sumesh
LEGAL REPRESENTATIVE: Nils H. Ljungman & Associates
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1703
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns an expressible nucleic acid construct, which contains only the sequence information necessary for expressing a gene for RNA or protein synthesis. Expression constructs of this type can be used in gene therapy and genetic vaccination and avoid many of the risks associated with constructs today. The invention further concerns the

possibility of improving the conveying of the construct into cells or tissue by covalent linkage of the construct, for example to particles or peptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 27 OF 47 USPATFULL

ACCESSION NUMBER:	2002:95541 USPATFULL
TITLE:	Method for screening compounds capable of inhibiting binding between the transcription factor of STAT1 and the transcription factor of USF1
INVENTOR(S):	Mach, Bernard, Chambesy, SWITZERLAND
PATENT ASSIGNEE(S):	Novimaune S.A., SWITZERLAND (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6379894	B1	20020430
APPLICATION INFO.:	US 2000-641999		20000818 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 1999-FR376, filed on 19 Feb 1999		

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1998-2025	19980219

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Horlick, Kenneth R.
LEGAL REPRESENTATIVE:	Lerner, David, Littenberg, Krumholz & Mentlik, LLP
NUMBER OF CLAIMS:	15
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	965

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns a method for determining whether a candidate compound is capable of inhibiting fixing between STAT1 and USF1 polypeptides comprising the following steps: (a) provide all or part of the STAT1 polypeptide capable of fixing with the USF1 polypeptide; (b) providing all or part of the USF1 polypeptide capable of fixing with the STAT1 polypeptide; (c) contacting said polypeptides as defined in (a) and (b) with one said candidate compound in conditions suitable for fixing between STAT1 and USF1 polypeptides; (d) measuring the fixing between the STAT1 and USF1 polypeptides; and (e) comparing said measurement with the fixing measurement between STAT1 and USF1 polypeptides in similar experimental conditions in the absence of said candidate compound, a decrease in fixing leading to conclude that said compound candidate is capable of inhibiting fixing between STAT1 and USF1 polypeptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 28 OF 47 USPATFULL

ACCESSION NUMBER:	2002:70008 USPATFULL
TITLE:	Methimazole derivatives and tautomeric cyclic thiones to treat autoimmune diseases
INVENTOR(S):	Kohn, Leonard D., Bethesda, MD, United States Curley, Robert W., Columbus, OH, United States Rice, John M., West Chester, OH, United States
PATENT ASSIGNEE(S):	Sentron Medical, Inc., Rockville, MD, United States (U.S. corporation) The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION: US 6365616 B1 20020402
APPLICATION INFO.: US 1999-382960 19990825 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-141311, filed on 31 Aug 1998, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Criares, Theofore J.
LEGAL REPRESENTATIVE: Frost Brown Todd LLC
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 17 Drawing Page(s)
LINE COUNT: 3028
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods for treating autoimmune diseases in mammals and for preventing or treating transplantation rejection in a transplant recipient. These methods utilize specifically-defined methimazole derivatives and tautomeric cyclic thione compounds, as well as pharmaceutical compositions containing those compounds. These compounds and compositions have been found to be at least as effective as methimazole in terms of pharmaceutical activity, while having less of an adverse affect on thyroid function. They are also more soluble in conventional pharmaceutical vehicles than methimazole. An assay for screening the activity of compounds useful against autoimmune diseases (ability to suppress expression of MHC Class I and II molecules) is also taught.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 29 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:423722 BIOSIS
DOCUMENT NUMBER: PREV200200423722
TITLE: **CIITA**-interacting proteins and methods of use therefor.
AUTHOR(S): Glimcher, Laurie H.; Zhou, Hong Yan (1)
CORPORATE SOURCE: (1) Wilmington, DE USA
ASSIGNEE: President and Fellows of Harvard College
PATENT INFORMATION: US 6410261 June 25, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 25, 2002) Vol. 1259, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

AB Isolated nucleic acid molecules encoding a novel protein, CIP104, that interacts with **CIITA**, an MHC class II transcriptional activator, are disclosed. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals carrying a CIP104 transgene. The invention further provides isolated CIP104 proteins and peptides, CIP104 fusion proteins and anti-CIP104 antibodies. Methods of using the CIP104 compositions of the invention are also disclosed, including methods for detecting CIP104 activity (e.g., CIP104 protein or mRNA) in a biological sample, methods of modulating CIP104 activity in a cell, and methods for identifying agents that modulate an interaction between CIP104 and **CIITA**.

L3 ANSWER 30 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:928873 CAPLUS
DOCUMENT NUMBER: 138:299406
TITLE: The phage .lambda. CII transcriptional activator carries a C-terminal domain signaling for rapid proteolysis
AUTHOR(S): Kobiler, Oren; Koby, Simi; Teff, Dinah; Court, Donald;

Oppenheim, Amos B.
CORPORATE SOURCE: Department of Molecular Genetics and Biotechnology, Hebrew University-Hadassah Medical School, Jerusalem, 91120, Israel
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(23), 14964-14969
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ATP-dependent proteases, like FtsH (HflB), recognize specific protein substrates. One of these is the .lambda. CII protein, which plays a key role in the phage lysis-lysogeny decision. Here we provide evidence that the conserved C-terminal end of CII acts as a necessary and sufficient cis-acting target for rapid proteolysis. Deletions of this conserved tag, or a mutation that confers two aspartic residues at its C terminus do not affect the structure or activity of CII. However, the mutations abrogate CII degrdn. by FtsH. We have established an in vitro assay for the .lambda. CIII protein and demonstrated that CIII directly inhibits proteolysis by FtsH to protect CII and CII mutants from degrdn. Phage .lambda. carrying mutations in the C terminus of CII show increased frequency of lysogenization, which indicates that this segment of CII may itself be sensitive to regulation that affects the lysis-lysogeny development. In addn., the region coding for the C-terminal end of CII overlaps with a gene that encodes a small **antisense** RNA called OOP. We show that deletion of the end of the cII gene can prevent OOP RNA, supplied in trans, interfering with CII activity. These findings provide an example of a gene that carries a region that modulates stability at the level of mRNA and protein.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 31 OF 47 USPATFULL
ACCESSION NUMBER: 2001:155766 USPATFULL
TITLE: 49 human secreted proteins
INVENTOR(S): Moore, Paul A., Germantown, MD, United States
Ruben, Steven M., Oley, MD, United States
Olsen, Henrik S., Gaithersburg, MD, United States
Shi, Yanggu, Gaithersburg, MD, United States
Rosen, Craig A., Laytonsville, MD, United States
Florence, Kimberly A., Rockville, MD, United States
Soppet, Daniel R., Centreville, VA, United States
Lafleur, David W., Washington, DC, United States
Endress, Gregory A., Potomac, MD, United States
Ebner, Reinhard, Gaithersburg, MD, United States
Komatsoulis, George, Silver Spring, MD, United States
Duan, Roxanne D., Bethesda, MD, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001021700	A1	20010913
APPLICATION INFO.:	US 2000-739254	A1	20001219 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-97917P	19980825 (60)
	US 1998-98634P	19980831 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23

EXEMPLARY CLAIM: 1
LINE COUNT: 15462
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 32 OF 47 USPATFULL
ACCESSION NUMBER: 2001:235085 USPATFULL
TITLE: Gene expression profiles in normal and cancer cells
INVENTOR(S): Vogelstein, Bert, Baltimore, MD, United States
Kinzler, Kenneth W., BelAir, MD, United States
Zhang, Lin, Baltimore, MD, United States
Zhou, Wei, Baltimore, MD, United States
PATENT ASSIGNEE(S): The JohnsHopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6333152	B1	20011225	
APPLICATION INFO.:	US 1998-81646		19980520	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Fredman, Jeffrey
LEGAL REPRESENTATIVE: Bannee & Witcoff
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 2244
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB As a step towards understanding the complex differences between normal and cancer cells, gene expression patterns were examined in gastrointestinal tumors. More than 300,000 transcripts derived from at least 45,000 different genes were analyzed. Although extensive similarity was noted between the expression profiles, more than 500 transcripts that were expressed at significantly different levels in normal and neoplastic cells were identified. These data provide insights into the extent of expression differences underlying malignancy and reveal genes that are useful as diagnostic or prognostic markers.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 33 OF 47 USPATFULL
ACCESSION NUMBER: 2001:231143 USPATFULL
TITLE: Arrays for identifying agents which mimic or inhibit the activity of interferons
INVENTOR(S): Silverman, Robert H., Beachwood, OH, United States
Williams, Bryan R. G., Cleveland, OH, United States
Der, Sandy, Cleveland, OH, United States
PATENT ASSIGNEE(S): The Cleveland Clinic Foundation, Cleveland, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6331396	B1	20011218	
APPLICATION INFO.:	US 1999-405438		19990923	(9)

	NUMBER	DATE

PRIORITY INFORMATION: US 1998-101497P 19980923 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Zitomer, Stephanie
ASSISTANT EXAMINER: Forman, B J
LEGAL REPRESENTATIVE: Calfee, Halter & Griswold LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 9639
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and model systems for identifying and characterizing new therapeutic agents, particularly proteins, which mimic or inhibit the activity of all interferons, Type I interferons, IFN-.alpha., IFN-.beta., or IFN-.gamma.. The method comprises administering an interferon selected from the group consisting of IFN-.alpha., IFN .beta., IFN-.tau., IFN-.omega., IFN-.gamma., and combinations thereof to cultured cells, administering the candidate agent to a duplicate culture of cells; and measuring the effect of the candidate agent and the interferon on the transcription or translation of one or, preferably, a plurality of the interferon stimulated genes or the interferon repressed genes (hereinafter referred to as "ISG's" and "IRGs", respectively). The model system is an array with gene probes that hybridize with from about 100 to about 5000 ISG and IRG transcripts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 34 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:277727 CAPLUS
DOCUMENT NUMBER: 132:318607
TITLE: Sequences of a novel transcription factor of MHC class II genes, substances capable of inhibiting this new transcription factor, and medical uses of said substances
INVENTOR(S): Masternak, Krzysztof; Reith, Walter; Mach, Bernard
PATENT ASSIGNEE(S): Novimmune S.A., Switz.
SOURCE: Eur. Pat. Appl., 48 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 995798	A1	20000426	EP 1998-120085	19981024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2000024766	A2	20000504	WO 1999-EP8026	19991022
WO 2000024766	A3	20000817		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1124953	A2	20010822	EP 1999-970995	19991022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002156258	A1	20021024	US 2001-840243	20010424

PRIORITY APPLN. INFO.: EP 1998-120085 A 19981024
WO 1999-EP8026 W 19991022

AB The invention provides sequences of a novel transcription factor of MHC

class II genes, inhibitors of this transcription factor capable of down-regulating the expression of MHC class II mols., and medical uses of these inhibitors. The novel transcription factor, called RFX-ANK, is a 33 kDa subunit of the RFX transcription complex, possesses a series of ankyrin repeats and a well defined protein-protein interaction motif, and is essential for binding the RFX complex to the conserved X box motif of MHC II promoters. The gene encoding RFX-ANK, which was mapped to 19p12, is capable of fully correcting the MHC II expression deficiency found in cell lines from patients having an autosomal recessive disease resulting from mutations in the regulatory genes responsible for the expression of MHC II genes. The invention further provides inhibitors of RFX-ANK, including antibodies, RFX-ANK mutants/derivs./fragments, **ribozymes** , and **antisense** mols. The inhibitors of the invention are also useful as immunosuppressants for the treatment and prevention of diseases assocd. with aberrant expression of MHC class II genes.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 35 OF 47 USPATFULL

ACCESSION NUMBER: 2000:105716 USPATFULL

TITLE: Methods of disrupting interferon signal transduction pathways

INVENTOR(S): Sedmak, Daniel, Columbus, OH, United States
Miller, Daniel, Hilliard, OH, United States
Rahill, Brian, Columbus, OH, United States
Zhang, Yingxue, Columbus, OH, United States

PATENT ASSIGNEE(S): Ohio State Research Foundation, Columbus, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6103531		20000815	
APPLICATION INFO.:	US 1999-249154		19990212	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-74575P	19980213	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schwartzman, Robert A.
ASSISTANT EXAMINER: Ousley, Andrea
LEGAL REPRESENTATIVE: Calfee, Halter & Griswold LLP
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 370

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for reducing levels of JAK 1 and thereby blocking the signal transduction pathways that are employed by IFN-.alpha., IFN-.beta., and IFN-.gamma. is provided. In one embodiment the method comprises the steps of: providing a cytomegalovirus (CMV) gene product selected from the group consisting of the CMV immediate early gene (IE) products, the CMV early gene (E) products, and combinations thereof; and introducing the CMV gene product or products into cells at levels sufficient to decrease the levels of JAK 1 in the cell. In another embodiment the method comprises the steps of providing a DNA molecule that comprises a CMV IE gene, a CMV E gene, or combinations thereof; introducing the DNA molecule into the cell; and inducing the expression of CMV IE and E genes in the cell, wherein the expression of products encoded by the CMV IE and CMV E genes decreases the levels of JAK 1 in the cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 36 OF 47 USPATFULL

ACCESSION NUMBER: 2000:40875 USPATFULL

TITLE: Human LIG-1 homolog (HLIG-1)

INVENTOR(S): Wu, Shujian, Levittown, PA, United States
Sweet, Raymond W, Bala Cynwyd, PA, United States
Truneh, Alemseged, West Chester, PA, United States
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6046030		20000404	
APPLICATION INFO.:	US 1997-986485		19971208	(8)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1997-59448P	19970922	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Caputa, Anthony C.
ASSISTANT EXAMINER: Gucker, Stephen
LEGAL REPRESENTATIVE: Han, William T.Ratner & Prestia, King, William T.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 2648
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB HLIG-1 polypeptides and polynucleotides and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing HLIG-1 polypeptides and polynucleotides in the design of protocols for the treatment of neurological disorders such as Alzheimer's disease, multiple sclerosis and abnormal neural development; endocrine disorders such as diabetes; and heart disease, among others and diagnostic assays for such conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 37 OF 47 USPATFULL
ACCESSION NUMBER: 2000:15639 USPATFULL
TITLE: Regulation of gene expression
INVENTOR(S): Peyman, John A., Cheshire, CT, United States
PATENT ASSIGNEE(S): Yale University, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6022863		20000208	
APPLICATION INFO.:	US 1996-646789		19960521	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Martinell, James
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 77
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 43 Drawing Figure(s); 28 Drawing Page(s)
LINE COUNT: 4750
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to utrons, RNA molecules which contain promoter regulatory motif(s) and DNA analogs thereof and DNA molecules that can be transcribed to produce the foregoing. In particular, the invention provides gene promoter suppressing nucleic acids which suppress transcription from a promoter of interest. In a preferred embodiment, the invention provides the TSU gene, nucleotide sequences of the TSU gene and RNA, as well as fragments, homologs and derivatives thereof. Methods of isolating TSU genes are also provided. Therapeutic and diagnostic methods and pharmaceutical compositions are also provided. In particular, the invention relates to methods for cell replacement therapy, gene therapy or organ transplantation wherein TSU nucleic acids suppress MHC class I and II gene expression, thus

preventing immuno-rejection of non-autologous cells or organs. The invention also provides methods for treatment of diseases or disorders by suppression of MHC class I, MHC class II, ICAM-1, B7-1, B7-2, and/or Fc.gamma.R expression by provision of TSU function.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 38 OF 47 USPATFULL

ACCESSION NUMBER:	2000:15517 USPATFULL
TITLE:	Regulatory genetic DNA that regulates the Class II transactivator (**CIITA**)
INVENTOR(S):	Ting, Jenny Pan-Yun, Chapel Hill, NC, United States Piskurich, Janet, Chapel Hill, NC, United States
PATENT ASSIGNEE(S):	University of North Carolina at Chapel Hill, Chapel Hill, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6022741		20000208
APPLICATION INFO.:	US 1997-816617		19970313 (8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	McKelvey, Terry
LEGAL REPRESENTATIVE:	Myers Bigel Sibley & Sajovec, P.A.
NUMBER OF CLAIMS:	40
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	8 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT:	1420

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel DNAs that regulate expression of the Class II Transactivator (**CIITA**) gene are disclosed. Recombinant DNA comprising **CIITA** regulatory elements operably associated with a heterologous DNA are also disclosed. Additionally, assay systems for identifying compounds that regulate expression of the class II major histocompatibility (MHC) antigens are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 39 OF 47 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2000:880065 CAPLUS
DOCUMENT NUMBER:	135:28808
TITLE:	Effects of **CIITA antisense** RNA on the expression of HLA class II molecules
AUTHOR(S):	Zhou, Caihong; Lu, Daru; Zhu, Qiquan; Qiu, Xinfang; Xue, Jinglun
CORPORATE SOURCE:	Institute of Genetics, Fudan University, Shanghai, 200433, Peop. Rep. China
SOURCE:	Chinese Science Bulletin (2000), 45(22), 2068-2071 CODEN: CSBUEF; ISSN: 1001-6538
PUBLISHER:	Science in China Press
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB To study the effect of the major histocompatibility complex class II (MHC II) transactivator (**CIITA**) **antisense** RNA on the expression of the human leukemia (HLA) class II mols., 5' end cDNA sequence of **CIITA** gene was cloned, and **antisense** RNA expression vector pcDNA-II was constructed. HeLa cells transfected with pcDNA-II and pcDNA3 were induced by IFN-.gamma. for 3 d. The expression of HLA class II mols. on HeLa/pcDNA-II cells was significantly decreased, while it has no effect on the expression of HLA class I mols. This result suggests that the **CIITA antisense** RNA can inhibit the expression of HLA class II mols. in HeLa cells. It also implies a promising approach to generate immune tolerance in graft transplantation.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:326045 CAPLUS
DOCUMENT NUMBER: 130:333755
TITLE: Human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators
INVENTOR(S): Glimcher, Laurie H.; Zhou, Hong
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9924570	A1	19990520	WO 1998-US22934	19981028
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002019514	A1	20020214	US 1997-965272	19971106
US 6410261	B2	20020625		
AU 9912861	A1	19990531	AU 1999-12861	19981028
AU 736150	B2	20010726		
EP 961828	A1	19991208	EP 1998-956308	19981028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001508313	T2	20010626	JP 1999-526487	19981028
US 2002146806	A1	20021010	US 2002-121882	20020412

PRIORITY APPLN. INFO.: US 1997-965272 A 19971106
WO 1998-US22934 W 19981028

AB Isolated nucleic acid mols. encoding a novel protein, CIP104, that interacts with **CIITA**, an MHC class II transcriptional activator, are disclosed. The invention further provides **antisense** nucleic acid mols., recombinant expression vectors contg. a nucleic acid mol. of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals carrying a CIP104 transgene. The invention further provides isolated CIP104 proteins and peptides, CIP104 fusion proteins and anti-CIP104 antibodies. Methods of using the CIP104 compns. of the invention are also disclosed, including methods for detecting CIP104 activity (e.g., CIP104 protein or mRNA) in a biol. sample, methods of modulating CIP104 activity in a cell, and methods for identifying agents that modulate an interaction between CIP104 and **CIITA**. Thus, a yeast two-hybrid assay was used to identify a cDNA encoding a **CIITA**-binding protein, CIP104. Northern blots showed CIP104 mRNA in most tissues examd., but thymus exhibited the highest level of expression. CIP104, in the presence of **CIITA**, activated expression of a reporter gene fused to the DR.alpha. promoter.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 41 OF 47 USPATFULL
ACCESSION NUMBER: 1999:63235 USPATFULL
TITLE: Transcription factor regulating MHC expression CDNA and genomic clones encoding same and retroviral expression constructs thereof
INVENTOR(S): Ono, Santa Jeremy, Baltimore, MD, United States
Strominger, Jack L., Lexington, MA, United States
PATENT ASSIGNEE(S): The Johns Hopkins University, Cambridge, MA, United

States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5908762		19990601
APPLICATION INFO.:	US 1997-828584		19970331 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-327832, filed on 21 Oct 1994		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Elliott, George C.		
ASSISTANT EXAMINER:	Schwartzman, Robert		
LEGAL REPRESENTATIVE:	Banner & Witcoff, Ltd.		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	26 Drawing Figure(s); 19 Drawing Page(s)		
LINE COUNT:	2266		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to NF-X1, a novel DNA binding protein which regulates expression of major histocompatibility complex (MHC) class II molecules, and to DNA sequences which encode the protein as well as recombinant expression of the protein. NF-X1 is a newly identified, cysteine-rich polypeptide which interacts sequence-specifically with the conserved X1 box regulatory element found in the proximal promoters of class II MHC genes. A cysteine-rich domain within NF-X1 contains a motif repeated seven times, and this entire region is necessary and sufficient for both sequence specific binding and effector function. The motif is related to but distinct from the previously described metal-binding protein families: LIM domain and RING finger. NFX.1 mRNA is markedly overexpressed late after induction of cells with interferon-gamma, and this overexpression coincides with a reduction in the level of HLA-DRA transcript in these cells. Overexpression of this protein strongly and specifically represses the transcription of the HLA-DRA gene in MHC class II positive cell lines, indicating that the NF-X1 protein is a transcriptional repressor of MHC class II molecules.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 42 OF 47 MEDLINE DUPLICATE 2

ACCESSION NUMBER:	2000069222 MEDLINE
DOCUMENT NUMBER:	20069222 PubMed ID: 10602887
TITLE:	Cancer immunotherapy by **antisense** suppression of Ii protein in MHC-class-II-positive tumor cells.
AUTHOR:	Qiu G; Goodchild J; Humphreys R E; Xu M
CORPORATE SOURCE:	Antigen Express Inc., One Innovation Drive, Worcester, MA 01605, USA.
SOURCE:	CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1999 Dec) 48 (9) 499-506. Journal code: 8605732. ISSN: 0340-7004.
PUB. COUNTRY:	GERMANY: Germany, Federal Republic of
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200001
ENTRY DATE:	Entered STN: 20000124 Last Updated on STN: 20000124 Entered Medline: 20000111

AB This study was aimed at creating a more effective tumor cell vaccine by suppressing Ii protein in the presence of MHC class II molecules within a cancer cell. Absence of the Ii protein, which normally blocks the antigenic-peptide-binding site of MHC class II molecules at synthesis in the endoplasmic reticulum, presumably increases the range of cancer-related epitopes presented to CD4+ helper T cells. Effective suppression of Ii protein was achieved with an **antisense**,

phosphorothioate oligonucleotide, which was selected on the basis of (1) the RNase H activation assay, (2) an assay for Ii protein suppression, and (3) a test for potency with respect to the extent of base sequence ("sequence walking"). The SaI murine sarcoma, which is MHC-class-I+ and MHC-class-II-, Ii-protein-, upon transfection with genes for either interferon gamma or the **MHC class II transactivator**, came to express MHC class II molecules and Ii protein. In each line of transfected tumor cells, the **antisense** oligonucleotide profoundly suppressed Ii protein in 35%-55% cells, without affecting expression of MHC class II molecules. Inoculation of mice with such Ii-protein-suppressed tumor vaccine cells, after either formaldehyde fixation or X-irradiation, led to much greater protection against challenge with the parental SaI sarcoma than did inoculation with untreated cells. This approach to cancer cell vaccination can be applied in a wide range of human tumors.

L3 ANSWER 43 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:239287 CAPLUS
DOCUMENT NUMBER: 128:281721
TITLE: Mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression
INVENTOR(S): Fabre, John William; Gustafsson, Kenth Tomas; Yun, Sheng
PATENT ASSIGNEE(S): Institute of Child Health, UK; Fabre, John William; Gustafsson, Kenth Tomas; Yun, Sheng
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815626	A2	19980416	WO 1997-GB2751	19971008
WO 9815626	A3	20000817		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9709030	A	19980423	ZA 1997-9030	19971008
AU 9745675	A1	19980505	AU 1997-45675	19971008

PRIORITY APPLN. INFO.:			
GB 1996-20940	A	19961008	
GB 1997-5911	A	19970321	
WO 1997-GB2751	W	19971008	

AB A polypeptide is provided that comprises the amino acid sequence of a class II trans activator (**CIITA**) protein from the N-terminus of which amino acid residues are missing such that the resulting polypeptide reduces the expression of MHC class II antigens. Deletion of the first 151 amino acids from the N-terminus of human **CIITA** results in strong suppression of MHC class II antigen synthesis both in cells that express the antigens constitutively and in cells that are susceptible to lymphokine induction of expression. The deletion polypeptide was expressed from a mutated cDNA which incorporated the first 6 codons (i.e., the start codon and the 5 codons corresponding to amino acids 2-6 of native human **CIITA**) at the 5'-end of the construct followed by a codon for isoleucine. The remainder of the construct comprises the codons for amino acid 152 to the end of the sequence. The mutant **CIITA** is useful in the treatment of autoimmune disease and in the prodn. of transgenic donor animals for xenografts and in the treatment of autoimmune diseases. A hammerhead **ribozymes** targeting bases 1159-1161 of

human **CIITA** are also useful, as are nucleic acids encoding the polypeptide and the **ribozyme**.

L3 ANSWER 44 OF 47 USPATFULL
ACCESSION NUMBER: 1998:147545 USPATFULL
TITLE: Transcription factor regulating MHC expression, CDNA and genomic clones encoding same and retroviral expression constructs thereof
INVENTOR(S): Ono, Santa Jeremy, Baltimore, MD, United States
Strominger, Jack L., Lexington, MA, United States
PATENT ASSIGNEE(S): The Johns Hopkins University, Baltimore, MD, United States (U.S. corporation)
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	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5840832		19981124	
APPLICATION INFO.:	US 1994-327832		19941021	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Wai, Thanda
LEGAL REPRESENTATIVE: Banner & Witcoff, Ltd.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 2119
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to NF-X1, a novel DNA binding protein which regulates expression of major histocompatibility complex (MHC) class II molecules, and to DNA sequences which encode the protein as well as recombinant expression of the protein. NF-X1 is a newly identified, cysteine-rich polypeptide which interacts sequence-specifically with the conserved X1 box regulatory element found in the proximal promoters of class II MHC genes. A cysteine-rich domain within NF-X1 contains a motif repeated seven times, and this entire region is necessary and sufficient for both sequence specific binding and effector function. The motif is related to but distinct from the previously described metal-binding protein families: LIM domain and RING finger. NFX.1 mRNA is markedly overexpressed late after induction of cells with interferon-gamma, and this overexpression coincides with a reduction in the level of HLA-DRA transcript in these cells. Overexpression of this protein strongly and specifically represses the transcription of the HLA-DRA gene in MHC class II positive cell lines, indicating that the NF-X1 protein is a transcriptional repressor of MHC class II molecules.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 45 OF 47 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 96322744 MEDLINE
DOCUMENT NUMBER: 96322744 PubMed ID: 8759739
TITLE: Stat1 alpha expression is involved in IFN-gamma induction of the class II transactivator and class II MHC genes.
AUTHOR: Lee Y J; Benveniste E N
CORPORATE SOURCE: Department of Cell Biology, University of Alabama at Birmingham 35294, USA.
CONTRACT NUMBER: AM-20614 (NIADDK)
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 Aug 15) 157 (4) 1559-68.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960924
Last Updated on STN: 19970203
Entered Medline: 19960917

AB Class II MHC Ags are critical in the regulation of immune responses by presenting Ag to T lymphocytes, resulting in their activation and differentiation. Class II expression is rare in the normal central nervous system, but elevated expression on glial cells has been observed in several neurologic diseases. We have previously demonstrated that IFN-gamma-induced class II expression in glial cells involves activation of both tyrosine kinase and protein kinase C. IFN-gamma induces tyrosine phosphorylation of the tyrosine kinases Jak1 and Jak2 and of Stat1 alpha. In addition, IFN-gamma enhances expression of Stat1 alpha mRNA and protein. We utilized **antisense** oligonucleotides against Stat1 alpha to determine directly whether IFN-gamma-induced activation and/or enhancement of Stat1 alpha is involved in class II expression. **Antisense** oligonucleotides complementary to Stat1 alpha mRNA were introduced in CH235-MG astroglioma cells by transient transfection; such treatment inhibited both constitutive and IFN-gamma-enhanced expression of Stat1 alpha. IFN-gamma-induced class II MHC expression was also inhibited in cells exposed to Stat1 alpha **antisense** oligonucleotides. The fact that the class II promoter does not contain IFN-gamma-activated sequences for binding Stat1 alpha suggests that Stat1 alpha must activate another protein that is directly involved in class II expression. A likely candidate is the class II MHC transactivator (**CIITA**). IFN-gamma induction of **CIITA** mRNA was also inhibited in cells treated with **antisense** oligonucleotides against Stat1 alpha. These findings demonstrate that Stat1 alpha is involved in IFN-gamma induction of **CIITA** expression, resulting in class II MHC expression.

L3 ANSWER 46 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:712099 CAPLUS
DOCUMENT NUMBER: 123:76446
TITLE: A gene for a transactivator (**CIITA**) of MHC class II antigen gene expression and uses of the transactivator gene
INVENTOR(S): Mach, Bernard Francois
PATENT ASSIGNEE(S): Switz.
SOURCE: Eur. Pat. Appl., 32 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 648836	A1	19950419	EP 1994-113378	19940826
EP 648836	B1	20020109		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 211763	E	20020115	AT 1994-113378	19940826
ES 2170082	T3	20020801	ES 1994-113378	19940826
US 5994082	A	19991130	US 1995-519547	19950825
JP 08224087	A2	19960903	JP 1995-219341	19950828
US 2002155542	A1	20021024	US 2002-104595	20020320

PRIORITY APPLN. INFO.:
EP 1993-113665 A 19930826
EP 1994-113378 A 19940826
US 1995-519547 A1 19950825
US 1999-413786 B1 19991007

AB Genes coding for transacting proteins essential for the general control of vertebrate MHC class II gene expression, and the proteins encoded by these genes and a method for the identification of such transacting proteins are described. Substances that limit or rectify the aberrant expression of MHC class II genes in the treatment of disease are disclosed. Expression

vectors for the manuf. of the transacting proteins and their use in the manuf. of the proteins are also disclosed. A cDNA for a transactivator was cloned by screening a cDNA bank for trans-complementation of the class II antigen regulatory mutant RJ2.25 leading to expression of an HLA-DR gene. The cloned cDNA was able to restore expression of MHC class II genes in cells from patients.

L3 ANSWER 47 OF 47 MEDLINE
ACCESSION NUMBER: 95323672 MEDLINE
DOCUMENT NUMBER: 95323672 PubMed ID: 7600294
TITLE: Molecular analysis of G1B and G3A IFN gamma mutants reveals that defects in **CIITA** or RFX result in defective class II MHC and Ii gene induction.
AUTHOR: Chin K C; Mao C; Skinner C; Riley J L; Wright K L; Moreno C S; Stark G R; Boss J M; Ting J P
CORPORATE SOURCE: Department of Biochemistry and Biophysics, University of North Carolina, Chapel Hill 27599-7260, USA.
CONTRACT NUMBER: AI29564 (NIAID)
AI34000 (NIAID)
CA37172 (NCI)
+
SOURCE: IMMUNITY, (1994 Nov) 1 (8) 687-97.
Journal code: 9432918. ISSN: 1074-7613.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950822
Last Updated on STN: 19950822
Entered Medline: 19950810

AB Class II major histocompatibility complex (MHC) genes and the invariant (Ii) gene are inducible by interferon-gamma (IFN gamma) but not by interferon-alpha and interferon-beta. The promoter regions of these genes contain three regulatory elements that mediate constitutive and IFN gamma-induced expressions; however, none of the DNA-binding proteins that interact with these elements are regulated by IFN gamma. Recently, a gene coding for a transactivator (**CIITA**) of class II MHC genes that complements a HLA-DR-negative immunodeficiency has been isolated. Using one IFN gamma mutant cell line (G3A) that is selectively defective in HLA-DR and Ii induction, four lines of evidence are presented to show that **CIITA** mediates the IFN gamma induction of HLA-DR and Ii genes. Analysis of another mutant line, G1B, indicates that the lack of DRA and Ii gene induction by IFN gamma is correlated with the lack of RFX DNA binding activity, thus providing the link between RFX and an IFN gamma response.

=> -
- IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d l3 ibib kwic tot

L3 ANSWER 1 OF 47 USPATFULL
ACCESSION NUMBER: 2003:127207 USPATFULL
TITLE: Transgenic animals and cells expressing proteins necessary for susceptibility to HIV infection
INVENTOR(S): Yoshiki, Takashi, Hokkaido, JAPAN
Lai, Yorong, Hokkaido, JAPAN
Ikeda, Hitoshi, Hokkaido, JAPAN
PATENT ASSIGNEE(S): GeneticLab Co., Ltd., Hokkaido, JAPAN (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003087420	A1	20030508
APPLICATION INFO.:	US 2002-176966	A1	20020621 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2001-191416	20010625

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY & LARDNER, P.O. Box 80278, San Diego, CA, 92138-0278
NUMBER OF CLAIMS: 60
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . CD4, a human chemokine receptor (such as CXCR4 or CCR5), a human cyclin T1, and a human class II transactivator (**CIITA**), and produce HIV virus particles. Also provided are methods of preparing the transgenic cells and rodent animals of the invention,. . .

SUMM . . . express major histocompatibility complex (MHC) class II molecules (M. Saifuddin et al., "Cutting Edge: Activation of HIV-1 Transcription by the **MHC Class II Transactivator**," J. Immunol., 164, 3941-3945 (2000); M. Saifuddin et al., "Expression of MHC Class II in T cells is associated with. . . forms the pTEFb complex together with CDK9 for the expression of target genes (S. Kanazawa et al., "Tat competes with **CIITA** for the binding to p-TEFb and blocks the expression of MHC class II genes in HIV infection," Immunity, 12, 61-70. . .

DRWD [0006] FIG. 1 provides a schematic illustration of three transgenes: pUC/CXCR4-CycT1, pUC/CycT1-CCR5, and pUC/**CIITA**-CD4.

DETD . . . human CD4, a human chemokine co-receptor (such as CXCR4 or CCR5), human cyclin T1, and a human class II transactivator (**CIITA**), and produce HIV virus particles. The animals and cells of the present invention are able to be infected by and. . .

DETD . . . "Induction of HIV-1 replication by allogenic stimulation," J. Immunol. 162, 7543-7548 (1995)). MHC class II gene expression is regulated by **CIITA**. In addition, **CIITA** has an acidic N-terminal activation domain and a C-terminal domain important for protein-protein interactions (H. Zhou et al., "Human MHC class II gene transcription directed by the carboxyl terminus of **CIITA**, one of the defective gene in type II MHC combined immune deficiency," Immunity 2, 545-553 (1995); K. C. Chin et. . . by binding hCyclin T1 and promotes HIV-1 expression in Tat independent activation. hCIITA which has about 70% homology to murine **CIITA** may also act a potential species-specific co-factor for HIV-1 replication. Indeed, double transfection of hCIITA and hCyclin T1 induced the. . .

DETD . . . ATGCCTGTCCAGAGCACAGCTGGGA
TCATC

.sup.aGenBank accession number: hCCR5, U54994; hCXCR4, Y14739; hCyclin T1, AF048730; hCIITA, NM000246.

.sup.b(+) means sense primer and (-) means **antisense** primer

DETD [0048] After linearization of each transgene, mixtures of Transgene 1 (pUC/CXCR4-CycT1) and 3 (pUC/**CIITA**-CD4) for T-tropic HIV-1 infection or of Transgene 2 (pUC/CycT1-CCR5) and 3 (pUC/**CIITA** -CD4) for M-tropic HIV-1 infection are microinjected into fertilized ova of female rats according to methods known in the art (e.g.,. . .

CLM What is claimed is:

. . . coding for an active portion of a human CyclinT1, and a nucleotide coding for an active portion of a human **CIITA**; incorporating each nucleotide into the genome of the rodent animal cell; stably expressing in the rodent animal cell an active. . .

. . . nucleotide coding for an active portion of human CyclinT1, and a nucleotide coding for an active portion of a human **CIITA**; and developing the embryonic cell to obtain a transgenic rodent animal capable of replicating HIV virus and producing HIV virus. . .

. . . the nucleotide coding for an active portion of human CyclinT1, and the nucleotide coding for an active portion of human **CIITA** are introduced into the embryonic cell on one or more plasmids.

. . . CD4, an active portion of human chemokine receptor, an active portion of human CyclinT1, and an active portion of human **CIITA**; infecting the transgenic animal with HIV; and monitoring the level of one or more indices selected from the group consisting. . .

L3 ANSWER 2 OF 47 USPATFULL

ACCESSION NUMBER:	2003:127128 USPATFULL
TITLE:	49 human secreted proteins
INVENTOR(S):	Moore, Paul A., Germantown, MD, UNITED STATES Ruben, Steven M., Olney, MD, UNITED STATES Olsen, Henrik S., Gaithersburg, MD, UNITED STATES Shi, Yanggu, Gaithersburg, MD, UNITED STATES Rosen, Craig A., Laytonsville, MD, UNITED STATES Florence, Kimberly A., Rockville, MD, UNITED STATES Soppet, Daniel R., Centreville, VA, UNITED STATES LaFleur, David W., Washington, DC, UNITED STATES Endress, Gregory A., Potomac, MD, UNITED STATES Ebner, Reinhard, Gaithersburg, MD, UNITED STATES Komatsoulis, George, Silver Spring, MD, UNITED STATES Duan, Roxanne D., Bethesda, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003087341	A1	20030508
APPLICATION INFO.:	US 2002-54988	A1	20020125 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-904615, filed on 16 Jul 2001, PENDING Continuation of Ser. No. US 2000-739254, filed on 19 Dec 2000, ABANDONED Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-97917P	19980825 (60)
	US 1998-98634P	19980831 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS:	23
EXEMPLARY CLAIM:	1
LINE COUNT:	19398

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0264] The translation product of this gene was shown to have homology to the classII MHC transactivator **CIITA** of Mus musculus (See, e.g., Genbank Accession No gi|1870520 and AAB48859.1; all references available through this accession are hereby incorporated. . . . MHC class II gene expression in B lymphocytes via direct interactation with the MHC class II-specific transcription factors. Furthermore, the **CIITA** protein is thought to play an indirect role in reducing tumorigenicity and inducing long-term tumor immunity.

SUMM [0651] In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or **antisense** DNA or RNA. **Antisense** techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as **Antisense** Inhibitors of Gene

Expression,CRCPress, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic. . . 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense**--Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design **antisense** or triple helix polynucleotides in an effort to treat or prevent disease.

SUMM . . . or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and **antisense** DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires. . .

SUMM . . . into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., **antisense** or **ribozymes**) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can. . .

SUMM [0844] **Antisense** and **Ribozyme** (Antagonists)

SUMM . . . SEQ ID NO: X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, **antisense** sequence is generated internally by the organism, in another embodiment, the **antisense** sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Anitsense Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). **Antisense** technology can be used to control gene expression through **antisense** DNA or RNA, or through triple-helix formation. **Antisense** techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla: (1988). Triple helix formation is discussed in, for instance, Lee et. . .

SUMM [0846] For example, the use of c-myc and c-myb **antisense** RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described.. . . A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given **antisense** RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked. . .

SUMM . . . coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an **antisense** RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The **antisense** RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

SUMM [0848] In one embodiment, the **antisense** nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an **antisense** nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the **antisense** nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired **antisense** RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral,. . .

SUMM [0849] The **antisense** nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a. . . sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded

antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or **triplex** formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the **antisense** nucleic acid Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or **triplex** as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of. . .

SUMM . . . to either the 5'- or 3'-non-translated, non-coding regions of a polynucleotide sequence of the invention could be used in an **antisense** approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. **Antisense** oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA, **antisense** nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50. . .

SUMM [0852] The **antisense** oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to,. . .

SUMM [0853] The **antisense** oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose,. . .

SUMM [0854] In yet another embodiment, the **antisense** oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a. . .

SUMM [0855] In yet another embodiment, the **antisense** oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the. . .

SUMM [0857] While **antisense** nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region. . .

SUMM [0858] Potential antagonists according to the invention also include catalytic RNA, or a **ribozyme** (See, e.g., PCT International Publication WO 90/11364, published Oct. 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While **ribozymes** that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs corresponding to the polynucleotides of the invention, the use of hammerhead **ribozymes** is preferred. Hammerhead **ribozymes** cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead **ribozymes** is well known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead **ribozyme** cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the **ribozyme** is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the. . .

SUMM [0859] As in the **antisense** approach, the **ribozymes** of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the **ribozyme** may be introduced into the cell in the same manner as described above for the introduction of **antisense** encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the **ribozyme** under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the **ribozyme** to destroy endogenous messages and

inhibit translation. Since **ribozymes** unlike **antisense** molecules, are catalytic, a lower intracellular concentration is required for efficiency.

SUMM . . . throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an **antisense** molecule directed to the polynucleotide of the present invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention. invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention

DETD . . . that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, **antisense**.

DETD [1132] In one example, **antisense** technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a. . . of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously **antisense** polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the **antisense** polynucleotide is provided in Example 23.

DETD . . . treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and **antisense** DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the. . .

L3 ANSWER 3 OF 47 USPATFULL

ACCESSION NUMBER:	2003:100088 USPATFULL		
TITLE:	Treatment methods based on microcompetition for a limiting GABP complex		
INVENTOR(S):	Polansky, Hanan, Rochester, NY, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003069199	A1	20030410
APPLICATION INFO.:	US 2002-219334	A1	20020815 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2000-732360, filed on 7 Dec 2000, PENDING		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Hanan Polansky, 3159 S. Winton Rd., Rochester, NY, 14623		
NUMBER OF CLAIMS:	26		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	28 Drawing Page(s)		
LINE COUNT:	14837		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . that the polynucleotides do not produce mRNA. If the sequences transcribe mRNA, block translation of proteins with, for instance, an **antisense** oligonucleotide specific for the exogenous mRNA. Alternatively, verify that the proteins are not involved in binding of F to either. . .

DETD . . . G0S7 oncogene fos; G0/G1 switch regulatory (ibid), Sato 1997
protein 7; v-fos FBJ murine osteosarcoma viral oncogene homolog; FOS; G0S7 (ibid)

C2TA **MHC2TA** **MHC class II transactivator; MHC2TA;** Goodman 2000
CIITA **CIITA** (ibid), Sisk 2000
C2TA (ibid)

AP1 JUN transcription factor AP-1; proto-oncogene Goodman

c-Jun (c-Jun); p39; v-jun avian sarcoma (ibid), Hottiger virus 17 oncogene homolog. . .

DETD [0543] Another aspect of the invention pertains to administration of a polynucleotide as **antisense**/antigene, **ribozyme**, triple helix, homologous nucleic acids, peptide nucleic acids, or microcompetitiors, equivalent polynucleotides, or homologous polynucleotides, isolated from, or substantially free. . .

DETD [0544] The following sections present standard protocols for the formulation of such polynucleotides. Since **antisense**/antigene, **ribozyme**, triple helix, homologous nucleic acids, peptide nucleic acids, and microcompetition agents are nucleic acid based, they share protocols for their. . .

DETD [0545] (a) **Antisense**/antigene

DETD [0546] In the present invention, the terms "**antisense**" and "antigene" polynucleotides is understood to include naturally or artificially generated polynucleotides capable of in situ binding to RNA or DNA, respectively. **Antisense** binding to mRNA may modify translation of bound mRNA, while antigene binding to DNA may modify transcription of bound DNA. **Antisense**/antigene binding may modify binding of a polypeptide of interest to RNA or DNA, for instance binding of an antigene to. . . cellular GABP to the foreign N-box resulting in attenuated microcompetition between the foreign polynucleotide and a cellular gene for GABP. **Antisense** /antigene binding may also modify, i.e., decrease or increase, expression of a polypeptide of interest.

DETD [0547] Binding, or hybridization of the **antisense**/antigene agent, may be achieved by base complementarity, or by interaction with the major groove of the cellular DNA duplex. The. . .

DETD [0548] The target of **antisense**/antigene agents has been thoroughly studied and is well known in the art. For instance, the **antisense** preferred target is the translational initiation site of a gene of interest, from approximately 10 nucleotides upstream to approximately 10. . . inhibitors of translation. Therefore, oligonucleotides targeting the 5' or 3' UTRs of a polynucleotide of interest may be used as **antisense** agents to inhibit translation. **Antisense** agents targeting the coding region are less effective inhibitors of translation but may be used when appropriate.

DETD . . . of complementarity is generally understood by those skilled in the art to be measured relative to the length of the **antisense** /antigene agent. In other words, three bases of mismatch in a 20 base oligonucleotide have a more profoundly detrimental effect than. . .

DETD [0550] Several methods are suitable for the delivery of **antisense**/antigene agents. In one exemplary embodiment, a recombinant expression plasmid is engineered to express **antisense** RNA following introduction into host cells. The RNA is complementary to a unique portion of DNA or mRNA sequence of interest. In an alternative embodiment, chemically derivatized synthetic oligonucleotides are used as **antisense**/antigene agents. Such oligonucleotides may contain modified nucleotides to attain increased stability once exposed to cellular nucleases. Examples of modified nucleotides. . .

DETD [0551] Whichever sequence of the polynucleotide of interest is targeted by **antisense**/antigene agents, in vitro studies should be undertaken first to determine the effectiveness and specificity of the agent. Control treatments should. . .

DETD [0552] **Antisense**/antigene agents can be oligonucleotides of RNA, DNA, mixtures of both, chemical derivatives of either, and single or double stranded. Nucleotides. . .

DETD . . . vivo, or other compounds which facilitate transport into the target cell are included. Additional compounds may be adducted to the **antisense**/antigene agent to enable crossing of the blood-brain barrier, cleavage of the target sequence upon binding, or to intercalate

in the duplex which results from hybridization to stabilize that complex. Any such modification, intended to increase effectiveness of the **antisense**/antigene agent, is included in the present invention.

DETD [0554] Similarly, the **antisense**/antigene agent may include modifications to the phosphate backbone including, but not limited to, phosphorothioates, phosphordamidate, methylphosphonate, and others. The agent. . .

DETD [0555] In another exemplary embodiment, the **antisense**/antigene agent is an alpha anomeric oligonucleotide capable of forming parallel, rather than antiparallel, hybrids with a cellular mRNA of interest.

DETD [0556] It is common for **antisense** agents to be targeted against the coding regions of an RNA of interest to effect translational inhibition. In a preferred embodiment, **antisense** agents are targeted instead against the transcribed but untranslated region of an RNA transcript. In this case, rather than achieving. . .

DETD [0557] For optimal efficacy, the **antisense**/antigene agents must be delivered to cells carrying the polynucleotide of interest in vivo. Several delivery methods are known in the art, including but not limited to, targeting techniques employing polypeptides linked to the **antisense**/antigene agent which bind to specific cellular receptors. In this instance the agents may be provided systemically. Alternatively the agents may. . .

DETD [0558] **Antisense**/antigene methodologies often face the problem of achieving sufficient intracellular concentration of the agent to effectively compete with cellular transcription and/or translation factors. To overcome this challenge, those skilled in the art introduce recombinant expression vectors carrying the **antisense**/antigene agent. Once introduced into the target cell, expression of the **antisense**/antigene agent from the incorporated RNA polymerase II or III promoter results in sufficient intracellular concentrations. Vectors can be chosen to. . . lost when the target cell divides. In either case, the primary goal is attaining levels of transcription that produce sufficient **antisense**/antigene agents to be effective. The choice of a suitable vector and the development of an effective **antisense** construct involves techniques standard in the art.

DETD [0559] **Antisense**/antigene expression man be regulated by any promoter known to be active in mammalian, especially human, cells and may be either. . . they may participate in microcompetition with cellular genes. In the case of inducible promoters, the biological effects of the expressed **antisense** can be discerned from any effect the promoter has on microcompetition by assaying any bioactivity with and without induced gene. . .

DETD [0560] **Antisense** agents may be prepared using any of a number of methods commonly known to those skilled in the art. In. . .

DETD [0561] Despite the ease of synthesis, the selection of effective **antisense** agents involves the identification of a suitable target for the agent. This process is simplified somewhat by the many software. . . from Premier Biosoft International or Primer 3, available online at http://www-genome.wi.mit.edu/cgi-bin/primer/primer3.cgi. Alternatively, a scientist skilled in the art may design **antisense** agents manually. Relevant aspects of the design process which need attention include selection of the target region to which the **antisense** agent will bind. Ideally it will be the gene promoter, if the target is DNA, or the translation initiation site. . .

DETD [0562] Longer **antisense** agents may be produced within the target cell from recombinant expression vectors. In one exemplary embodiment, the desired **antisense**-encoding sequences can be incorporated into an appropriate expression vector selected because it contains the regulatory sequences necessary to ensure expression in the target cell type. Selection of the sequence composition of the **antisense** agent must take into account the same considerations used to design shorter oligonucleotides as described in the previous paragraph including,. . .

DETD [0563] Control agents, whether synthetic oligonucleotides or longer **antisense** agents expressed in vivo by expression vectors, are employed to validate the efficacy and specificity of the therapeutic agents. Each. . .

DETD [0567] Delivery of Oligonucleotides: Methods for effective administration of **antisense** agents vary with the agent used. In one exemplary embodiment, synthetic oligonucleotides are delivered by simple diffusion into the target. . .

DETD . . . mediated transfection as described by Daftary and Taylor (2001.sup.137). This method enhances diffusion into the target cell by encasing the **antisense** agent in a lipophilic liposome. However, this method too has drawbacks. While cellular uptake is enhanced, the ratio of liposome. . .

DETD [0569] In another exemplary embodiment, **antisense** expressing viral vectors may be used to confer target cell specificity. In some cases, viral delivery agents may be selected. . .

DETD [0570] (b) **Ribozymes**

DETD [0571] While **antisense** agents act by either inhibiting transcription or translation of the target gene, or by inducing enzyme-mediated transcript degradation by RNase H or a similar enzyme, **ribozymes** offer an alternative approach. **Ribozymes** are RNA molecules which natively bind to and cleave target transcripts. Typical **ribozymes** bind to and cleave RNA at specific sites, however hammerhead **ribozymes** cleave target transcripts at sites directed by flanking nucleotide sequences which bind to the target site. The use of hammerhead **ribozymes** is preferred because the only sequence requirement for their activity is the UG dinucleotide arranged in the 5'-3' orientation. Hammerhead. . . in the art (see, for example Doherty 2001.sup.138, or Goodchild 2000.sup.139). In a preferred embodiment, the sequence targeted by the **ribozyme** lies near the 5' end of the transcript. That will result cleavage of the transcript near the translation initiation site. . .

DETD [0572] **Ribozymes** identified in Tetrahymena thermophila, which employ an eight base pair active site which duplexes with the target RNA molecule; are included in this invention. This invention includes those **ribozymes**, described and characterized by Cech and coworkers (i.e. IVS or L-19IVS RNA), which target eight base-pair sequences in a gene. . . For the catalytic sequence of these agents see, for instance, U.S. Pat. No. 5,093,246, incorporated entirely herein by reference. Any **ribozyme** or hammerhead **ribozyme** molecules that target RNA sequences expressed by a foreign polynucleotide, disrupted gene or gene in a disrupted pathway, are included. . .

DETD [0573] **Ribozymes**, being RNA molecules of specific sequence, may be synthesized with modified nucleotides which enable better targeting to the host cell of interest or which improve stability. As described above for conventional **antisense** agents, the preferred method of delivery involves introduction into the target cell, a recombinant expression vector encoding the ribosome. Inclusion. . . cleave and disrupt transcripts of foreign DNA or disrupted genes or genes in a disrupting pathway. The catalytic nature of **ribozymes** permits their effective use at concentrations below those needed for traditional **antisense** agents.

DETD [0574] Identification of **ribozyme** cleavage sites within a transcript of interest is accomplished with any of a number of computer algorithms which scan linear. . . well known in the art, for their potential to form secondary structures which may interfere with the action of targeted **ribozyme** agents. Alternatively, empirical assays employing ribonucleases may be used to probe the accessibility of identified target sequences.

DETD [0575] **Ribozymes** comprise a unique class of oligonucleotides which bind to specific ribonucleic acid targets and promote their hydrolysis. The design of **ribozyme** agents is well known to those skilled in the art. In order to prepare effective **ribozyme** agents, initially a suitable target sequence must be identified which

confers specificity to the agent in order to minimize unwanted side effects and maximize efficacy. Once that target is identified the **ribozyme** agent is synthesized using standard oligonucleotide synthesis procedures such as those exemplified herein. Delivery to the target cell may be. . .

DETD [0576] Ensuring the purity and efficacy of **ribozyme** agents may be more important than for other nucleic acid agents because their intended effects, namely the hydrolysis of target. . . extensive preclinical testing is essential to minimize unwanted side effects. These risks are, however, outweighed by the potential effectiveness of **ribozyme** agents.

DETD . . . purines within the target sequence and vice versa, which inhibit transcription of the target sequence. The effectiveness of a targeted **triplex** forming oligonucleotide may be enhanced by including a "switchback" motif composed of alternating 5'-3' and 3'-5' regions of purines and. . .

DETD [0580] **Triplex** agent formulation begins with selection of an appropriate target sequence within the cells to be treated. That target may be. . . the target is double stranded DNA, the most effective targets surround and include the transcriptional regulatory regions. Formation of a **triplex** between the agent and the target will inhibit the binding of RNA polymerase or other requisite transcriptional regulatory factors which. . .

DETD [0581] **Triplex** agents may be synthesized to be more resistant to cellular and extracellular nucleases by the inclusion of modified nucleotides such. . . of the base intercalating agent acridine, may be incorporated into the therapeutic agent to restore desirable binding properties to the **triplex** forming oligonucleotide. Alternatively, if the intracellular target is an mRNA, C-5 propyne pyrimidines may be included in the synthetic oligophosphorothioate. . .

DETD [0582] The affinity of **triplex** agents for their respective targets may be assessed by electrophoretic gel retardation assays. The formation of **triplex** structures will retard migration through an electrophoretic gel. Similarly, UV melting experiments can assess the stability of any **triplex** agent binding to its target. In these assays **triplex** agents are mixed with their intended target in vitro and the resulting triplexes are heated (with, for example, a Haake cryothermostat) while monitoring their UV absorbance (with, for example, a Kontron-Uvikon 940 spectrophotometer) (on design of **triplex** forming oligonucleotides see, for instance, Francois (1999.sup.140)).

DETD [0583] **Triplex** forming agents are simply oligonucleotides designed to form triple helices with the target intracellular nucleic acid. Accordingly, their synthesis, purification. . .

DETD [0593] Oligonucleotides so modified can be used in the same therapeutic techniques as unmodified homologs. They can be used as **antisense** agents designed to interfere with the expression of a foreign polynucleotide, a disrupted gene, or a gene in a disrupted. . .

DETD [0795] **C2TA** (P33076 AF410154 U18259 U18288 U31931 X74301)

DETD . . . or extracellular proteins in vivo. Compounds that interfere with, or disrupt the binding may include, but are not limited to, **antisense** oligonucleotides, antibodies, peptides, and similar molecules.

DETD . . . isolated, amplified, if necessary, digested with one or several restriction endonucleases, and the fragments separated by gel electrophoresis. Sequence specific **ribozymes** are then used to detect specific mutations by development or loss of a **ribozyme** cleavage site.

DETD [1017] Oligonucleotide agents, e.g. **antisense** oligonucleotides or recombinant expression vectors, may be formulated for localized or systemic administration. Systemic administration may be achieved by injection. . .

DETD [1339] NIH3T3 cells were transfected with a vector expressing BRCA1 **antisense** RNA resulting in reduced expression of endogenous BRCA1 protein. The transfected cells, unlike parental and sense

transfectants, showed accelerated growth. . .

DETD . . . an overall reduction in the copy number of viral genomes present, or by inhibition of viral N-boxes (for instance by **antisense**), etc. The reduced number of active viral N-boxes eases microcompetition and consequently slows progression of the microcompetition diseases.

DETD [2154] .sup.37 Sisk T J, Gourley T, Roys S, Chang C H. **MHC class II transactivator** inhibits IL-4 gene transcription by competing with NF-AT to bind the coactivator CREB binding protein (CBP)/p300. J Immunol. 2000 Sep. . .

DETD [2253] .sup.136 Deshmukh, R. R., Cole, D. L. and Sanghvi, Y. S. Purification of **Antisense** Oligonucleotides in Methods in Enzymology, ed. M. Ian Phillips, v313, 1999, Academic Press, pp203-226.

DETD [2255] .sup.138 Doherty, E. A and Doudna. **Ribozyme** structures and mechanisms. J.A. Ann. Rev. Biophys. Biomol Struct. 30, 457-475, 2001.

DETD [2256] .sup.139 Goodchild, J. Hammerhead **ribozymes**: biochemical and chemical considerations. Curr. Opin. Mol. Ther 2, 272-281, 2000. Review.

DETD [2257] .sup.140 Francois, J.-C., Lacoste, J., Lacroix, L. and J.-L. Mergny. Design of **Antisense** and **Triplex**-Forming Oligonucleotides. In Methods in Enzymology, ed. M Ian Phillips, v313, 1999, Academic Press, pp74-95

DETD [2260] .sup.143 Nielsen, P. E. (1999) **Antisense** Properties of Peptide Nucleic Acid. In Methods in Enzymology, ed. M. Ian Phillips, v313. 1999, Academic Press Academic Press, pp. . .

DETD [2288] .sup.171 Cohen A S, Smisek D L, Wang B H. Emerging technologies for sequencing **antisense** oligonucleotides: capillary electrophoresis and mass spectrometry. Adv Chromatogr. 1996;36:127-62. Review.

DETD [2401] .sup.284 Rao V N, Shao N, Ahmad M, Reddy E S. **Antisense** RNA to the putative tumor suppressor gene BRCA1 transforms mouse fibroblasts. Oncogene. 1996 Feb 1;12(3):523-8.

DETD . . . oxidized LDL (LOX-I) by oxidized LDL and implications in apoptosis of human coronary artery endothelial cells: evidence from use of **antisense** LOX-1 mRNA and chemical inhibitors. Arterioscler Thromb Vasc Biol. 2000 Apr;20(4): 1116-22.

L3 ANSWER 4 OF 47 USPATFULL

ACCESSION NUMBER: 2003:99511 USPATFULL

TITLE: Drug discovery assays based on microcompetition for a limiting GABP complex

INVENTOR(S): Polansky, Hanan, Rochester, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003068616	A1	20030410
APPLICATION INFO.:	US 2002-223050	A1	20020814 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-732360, filed on 7 Dec 2000, PENDING

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Hanan Polansky, 3159 S. Winton Rd., Rochester, NY, 14623

NUMBER OF CLAIMS: 55

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 28 Drawing Page(s)

LINE COUNT: 14981

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . that the polynucleotides do not produce mRNA. If the sequences transcribe mRNA, block translation of proteins with, for instance, an **antisense** oligonucleotide specific for the exogenous mRNA. Alternatively, verify that the proteins are not involved in binding of F to either. . .

DETD . . . oncogene fos; G0/G1 (ibid), Sato

		switch regulatory protein 7; v-fos FBJ murine osteo-sarcoma viral oncogene homolog; FOS; G0S7	1997 (ibid)
C2TA	**MHC2TA**	**MHC class**	
	II transactivator;	Goodman 2000	
	CIITA	**MHC2TA; CIITA**	
	(ibid), Sisk		
	C2TA		2000 (ibid)
AP1	JUN	transcription factor AP-1; proto-oncogene c-Jun (c-Jun); p39; v-jun avian sarcoma virus. . .	Goodman 2000 (ibid), Hottiger 2000 (ibid)

DETD [0517] Another aspect of the invention pertains to administration of a polynucleotide as **antisense**/antigene, **ribozyme**, triple helix, homologous nucleic acids, peptide nucleic acids, or microcompetitiors, equivalent polynucleotides, or homologous polynucleotides, isolated from, or substantially free. . .

DETD [0518] The following sections present standard protocols for the formulation of such polynucleotides. Since **antisense**/antigene, **ribozyme**, triple helix, homologous nucleic acids, peptide nucleic acids, and microcompetition agents are nucleic acid based, they share protocols for their. . .

DETD [0519] (a) **Antisense**/Antigene

DETD [0520] In the present invention, the terms "**antisense**" and "antigene" polynucleotides is understood to include naturally or artificially generated polynucleotides capable of in situ binding to RNA or DNA, respectively. **Antisense** binding to mRNA may modify translation of bound mRNA, while antigene binding to DNA may modify transcription of bound DNA. **Antisense**/antigene binding may modify binding of a polypeptide of interest to RNA or DNA, for instance binding of an antigene to. . . cellular GABP to the foreign N-box resulting in attenuated microcompetition between the foreign polynucleotide and a cellular gene for GABP. **Antisense** /antigene binding may also modify, i.e., decrease or increase, expression of a polypeptide of interest.

DETD [0521] Binding, or hybridization of the **antisense**/antigene agent, may be achieved by base complementarity, or by interaction with the major groove of the cellular DNA duplex. The techniques and conditions for achieving such interactions are well known in the art. The target of **antisense**/antigene agents has been thoroughly studied and is well known in the art. For instance, the **antisense** preferred target is the translational initiation site of a gene of interest, from approximately 10 nucleotides upstream to approximately 10. . . inhibitors of translation. Therefore, oligonucleotides targeting the 5' or 3' UTRs of a polynucleotide of interest may be used as **antisense** agents to inhibit translation. **Antisense** agents targeting the coding region are less effective inhibitors of translation but may be used when appropriate.

DETD . . . of complementarity is generally understood by those skilled in the art to be measured relative to the length of the **antisense** /antigene agent. In other words, three bases of mismatch in a 20 base oligonucleotide have a more profoundly detrimental effect than. . .

DETD [0523] Several methods are suitable for the delivery of **antisense**/antigene agents. In one exemplary embodiment, a recombinant expression plasmid is engineered to express **antisense** RNA following introduction into host cells. The RNA is complementary to a unique portion of DNA or mRNA sequence of interest. In an alternative embodiment, chemically derivatized synthetic oligonucleotides are used as **antisense**/antigene agents. Such oligonucleotides may contain modified nucleotides to attain increased stability once exposed to cellular nucleases. Examples of modified nucleotides. . .

DETD [0524] Whichever sequence of the polynucleotide of interest is targeted

by **antisense**/antigene agents, in vitro studies should be undertaken first to determine the effectiveness and specificity of the agent. Control treatments should. . .

DETD [0525] **Antisense**/antigene agents can be oligonucleotides of RNA, DNA, mixtures of both, chemical derivatives of either, and single or double stranded. Nucleotides. . .

DETD . . . vivo, or other compounds which facilitate transport into the target cell are included. Additional compounds may be adducted to the **antisense**/antigene agent to enable crossing of the blood-brain barrier, cleavage of the target sequence upon binding, or to intercalate in the duplex which results from hybridization to stabilize that complex. Any such modification, intended to increase effectiveness of the **antisense**/antigene agent, is included in the present invention.

DETD [0527] Similarly, the **antisense**/antigene agent may include modifications to the phosphate backbone including, but not limited to, phosphorothioates, phosphordamidate, methylphosphonate, and others. The agent. . .

DETD [0528] In another exemplary embodiment, the **antisense**/antigene agent is an alpha anomeric oligonucleotide capable of forming parallel, rather than antiparallel, hybrids with a cellular mRNA of interest.

DETD [0529] It is common for **antisense** agents to be targeted against the coding regions of an RNA of interest to effect translational inhibition. In a preferred embodiment, **antisense** agents are targeted instead against the transcribed but untranslated region of an RNA transcript. In this case, rather than achieving. . .

DETD [0530] For optimal efficacy, the **antisense**/antigene agents must be delivered to cells carrying the polynucleotide of interest in vivo. Several delivery methods are known in the art, including but not limited to, targeting techniques employing polypeptides linked to the **antisense**/antigene agent which bind to specific cellular receptors. In this instance the agents may be provided systemically. Alternatively the agents may. . .

DETD [0531] **Antisense**/antigene methodologies often face the problem of achieving sufficient intracellular concentration of the agent to effectively compete with cellular transcription and/or translation factors. To overcome this challenge, those skilled in the art introduce recombinant expression vectors carrying the **antisense**/antigene agent. Once introduced into the target cell, expression of the **antisense**/antigene agent from the incorporated RNA polymerase II or III promoter results in sufficient intracellular concentrations. Vectors can be chosen to. . . lost when the target cell divides. In either case, the primary goal is attaining levels of transcription that produce sufficient **antisense**/antigene agents to be effective. The choice of a suitable vector and the development of an effective **antisense** construct involves techniques standard in the art.

DETD [0532] **Antisense**/antigene expression man be regulated by any promoter known to be active in mammalian, especially human, cells and may be either. . . they may participate in microcompetition with cellular genes. In the case of inducible promoters, the biological effects of the expressed **antisense** can be discerned from any effect the promoter has on microcompetition by assaying any bioactivity with and without induced gene. . .

DETD [0533] **Antisense** agents may be prepared using any of a number of methods commonly known to those skilled in the art. In. . .

DETD [0534] Despite the ease of synthesis, the selection of effective **antisense** agents involves the identification of a suitable target for the agent. This process is simplified somewhat by the many software. . . from Premier Biosoft International or Primer 3, available online at http://www-genome.wi.mit.edu/cgi-bin/primer/primer3.cgi. Alternatively, a scientist skilled in the art may design **antisense** agents manually. Relevant aspects of the design process which need attention include selection of the target region to which the **antisense** agent will bind. Ideally it will be the gene promoter, if the target is DNA, or the translation

initiation site. . .

DETD [0535] Longer **antisense** agents may be produced within the target cell from recombinant expression vectors. In one exemplary embodiment, the desired **antisense**-encoding sequences can be incorporated into an appropriate expression vector selected because it contains the regulatory sequences necessary to ensure expression in the target cell type. Selection of the sequence composition of the **antisense** agent must take into account the same considerations used to design shorter oligonucleotides as described in the previous paragraph including,. . .

DETD [0536] Control agents, whether synthetic oligonucleotides or longer **antisense** agents expressed in vivo by expression vectors, are employed to validate the efficacy and specificity of the therapeutic agents. Each. . .

DETD [0540] Delivery of Oligonucleotides: Methods for effective administration of **antisense** agents vary with the agent used. In one exemplary embodiment, synthetic oligonucleotides are delivered by simple diffusion into the target. . .

DETD . . . mediated transfection as described by Daftary and Taylor (2001.sup.137). This method enhances diffusion into the target cell by encasing the **antisense** agent in a lipophilic liposome. However, this method too has drawbacks. While cellular uptake is enhanced, the ratio of liposome. . .

DETD [0542] In another exemplary embodiment, **antisense** expressing viral vectors may be used to confer target cell specificity. In some cases, viral delivery agents may be selected. . .

DETD [0543] (b) **Ribozymes**

DETD [0544] While **antisense** agents act by either inhibiting transcription or translation of the target gene, or by inducing enzyme-mediated transcript degradation by RNase H or a similar enzyme, **ribozymes** offer an alternative approach. **Ribozymes** are RNA molecules which natively bind to and cleave target transcripts. Typical **ribozymes** bind to and cleave RNA at specific sites, however hammerhead **ribozymes** cleave target transcripts at sites directed by flanking nucleotide sequences which bind to the target site. The use of hammerhead **ribozymes** is preferred because the only sequence requirement for their activity is the UG dinucleotide arranged in the 5'-3' orientation. Hammerhead. . . in the art (see, for example Doherty 2001.sup.138, or Goodchild 2000.sup.139). In a preferred embodiment, the sequence targeted by the **ribozyme** lies near the 5' end of the transcript. That will result cleavage of the transcript near the translation initiation site. . .

DETD [0545] **Ribozymes** identified in Tetrahymena thermophila, which employ an eight base pair active site which duplexes with the target RNA molecule, are included in this invention. This invention includes those **ribozymes**, described and characterized by Cech and coworkers (i.e. IVS or L-191VS RNA), which target eight base-pair sequences in a gene. . . For the catalytic sequence of these agents see, for instance, U.S. Pat. No. 5,093,246, incorporated entirely herein by reference. Any **ribozyme** or hammerhead **ribozyme** molecules that target RNA sequences expressed by a foreign polynucleotide, disrupted gene or gene in a disrupted pathway, are included. . .

DETD [0546] **Ribozymes**, being RNA molecules of specific sequence, may be synthesized with modified nucleotides which enable better targeting to the host cell of interest or which improve stability. As described above for conventional **antisense** agents, the preferred method of delivery involves introduction into the target cell, a recombinant expression vector encoding the ribosome. Inclusion. . . cleave and disrupt transcripts of foreign DNA or disrupted genes or genes in a disrupting pathway. The catalytic nature of **ribozymes** permits their effective use at concentrations below those needed for traditional **antisense** agents.

DETD [0547] Identification of **ribozyme** cleavage sites within a transcript of interest is accomplished with any of a number of computer

algorithms which scan linear. . . well known in the art, for their potential to form secondary structures which may interfere with the action of targeted **ribozyme** agents. Alternatively, empirical assays employing ribonucleases may be used to probe the accessibility of identified target sequences.

DETD [0548] **Ribozymes** comprise a unique class of oligonucleotides which bind to specific ribonucleic acid targets and promote their hydrolysis. The design of **ribozyme** agents is well known to those skilled in the art. In order to prepare effective **ribozyme** agents, initially a suitable target sequence must be identified which confers specificity to the agent in order to minimize unwanted side effects and maximize efficacy. Once that target is identified the **ribozyme** agent is synthesized using standard oligonucleotide synthesis procedures such as those exemplified herein. Delivery to the target cell may be. . .

DETD [0549] Ensuring the purity and efficacy of **ribozyme** agents may be more important than for other nucleic acid agents because their intended effects, namely the hydrolysis of target. . . extensive preclinical testing is essential to minimize unwanted side effects. These risks are, however, outweighed by the potential effectiveness of **ribozyme** agents.

DETD . . . purines within the target sequence and vice versa, which inhibit transcription of the target sequence. The effectiveness of a targeted **triplex** forming oligonucleotide may be enhanced by including a "switchback" motif composed of alternating 5'-3' and 3'-5' regions of purines and. . .

DETD [0553] **Triplex** agent formulation begins with selection of an appropriate target sequence within the cells to be treated. That target may be. . . the target is double stranded DNA, the most effective targets surround and include the transcriptional regulatory regions. Formation of a **triplex** between the agent and the target will inhibit the binding of RNA polymerase or other requisite transcriptional regulatory factors which. . .

DETD [0554] **Triplex** agents may be synthesized to be more resistant to cellular and extracellular nucleases by the inclusion of modified nucleotides such. . . of the base intercalating agent acridine, may be incorporated into the therapeutic agent to restore desirable binding properties to the **triplex** forming oligonucleotide. Alternatively, if the intracellular target is an mRNA, C-5 propyne pyrimidines may be included in the synthetic oligophosphorothioate. .

DETD [0555] The affinity of **triplex** agents for their respective targets may be assessed by electrophoretic gel retardation assays. The formation of **triplex** structures will retard migration through an electrophoretic gel. Similarly, UV melting experiments can assess the stability of any **triplex** agent binding to its target. In these assays **triplex** agents are mixed with their intended target in vitro and the resulting triplexes are heated (with, for example, a Haake cryothermostat) while monitoring their UV absorbance (with, for example, a Kontron-Uvikon 940 spectrophotometer) (on design of **triplex** forming oligonucleotides see, for instance, Francois (1999.sup.140)).

DETD [0556] **Triplex** forming agents are simply oligonucleotides designed to form triple helices with the target intracellular nucleic acid. Accordingly, their synthesis, purification. . .

DETD [0566] Oligonucleotides so modified can be used in the same therapeutic techniques as unmodified homologs. They can be used as **antisense** agents designed to interfere with the expression of a foreign polynucleotide, a disrupted gene, or a gene in a disrupted. . .

DETD [0766] **C2TA** (P33076 AF410154 U18259 U18288 U31931 X74301)

DETD . . . or extracellular proteins in vivo. Compounds that interfere with, or disrupt the binding may include, but are not limited to, **antisense** oligonucleotides, antibodies, peptides, and similar molecules.

DETD . . . isolated, amplified, if necessary, digested with one or several restriction endonucleases, and the fragments separated by gel

electrophoresis. Sequence specific **ribozymes** are then used to detect specific mutations by development or loss of a **ribozyme** cleavage site.

DETD [0989] Oligonucleotide agents, e.g. **antisense** oligonucleotides or recombinant expression vectors, may be formulated for localized or systemic administration. Systemic administration may be achieved by injection. . .

DETD [1316] NIH3T3 cells were transfected with a vector expressing BRCA1 **antisense** RNA resulting in reduced expression of endogenous BRCA1 protein. The transfected cells, unlike parental and sense transfectants, showed accelerated growth. . .

DETD . . . an overall reduction in the copy number of viral genomes present, or by inhibition of viral N-boxes (for instance by **antisense**), etc. The reduced number of active viral N-boxes eases microcompetition and consequently slows progression of the microcompetition diseases.

DETD [2134] .sup.37 Sisk T J, Gourley T, Roys S, Chang C H. **MHC class II transactivator** inhibits IL-4 gene transcription by competing with NF-AT to bind the coactivator CREB binding protein (CBP)/p300. J. Immunol. Sep. 1,. . .

DETD [2233] .sup.136 Deshmukh, R. R., Cole, D. L. and Sanghvi, Y. S. Purification of **Antisense** Oligonucleotides in Methods in Enzymology, ed. M. Ian Phillips, v313, 1999, Academic Press, pp203-226.

DETD [2235] .sup.138 Doherty, E. A and Doudna. **Ribozyme** structures and mechanisms. J. A. Ann. Rev. Biophys. Biomol Struct. 30, 457-475, 2001.

DETD [2236] .sup.139 Goodchild, J. Hammerhead **ribozymes**: biochemical and chemical considerations. Curr. Opin. Mol. Ther 2, 272-281, 2000. Review.

DETD [2237] .sup.140 Francois, J. -C., Lacoste, J., Lacroix, L. and J.-L. Mergny. Design of **Antisense** and **Triplex**-Forming Oligonucleotides. In Methods in Enzymology, ed. M Ian Phillips, v313, 1999, Academic Press, pp74-95

DETD [2240] .sup.143 Nielsen, P. E. (1999) **Antisense** Properties of Peptide Nucleic Acid. In Methods in Enzymology, ed. M. Ian Phillips, v313. 1999, Academic Press Academic Press, pp156-164.

DETD [2268] .sup.171 Cohen A S, Smisek D L, Wang B H. Emerging technologies for sequencing **antisense** oligonucleotides: capillary electrophoresis and mass spectrometry. Adv Chromatogr. 1996;36: 127-62. Review.

DETD [2381] .sup.284 Rao V N, Shao N, Ahmad M, Reddy E S. **Antisense** RNA to the putative tumor suppressor gene BRCA1 transforms mouse fibroblasts. Oncogene. Feb. 1, 1996;12(3):523-8.

DETD . . . oxidized LDL (LOX-1) by oxidized LDL and implications in apoptosis of human coronary artery endothelial cells: evidence from use of **antisense** LOX-1 mRNA and chemical inhibitors. Arterioscler Thromb Vasc Biol. 2000 April;20(4): 1116-22.

L3 ANSWER 5 OF 47 USPATFULL

ACCESSION NUMBER:	2003:78472 USPATFULL
TITLE:	Design principle for the construction of expression constructs for gene therapy
INVENTOR(S):	Wittig, Burghardt, Berlin, GERMANY, FEDERAL REPUBLIC OF Junghans, Claas, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S):	SOFT GENE GMBH (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003054392	A1	20030320
APPLICATION INFO.:	US 2002-228811	A1	20020827 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-310842, filed on 12 May 1999, GRANTED, Pat. No. US 6451593		

	NUMBER	DATE

PRIORITY INFORMATION: DE 1996-19648625 19961113
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: NILS H. LJUNGMAN, NILS H. LJUNGMAN & ASSOCIATES, P.O. BOX 130, GREENSBURG, PA, 15601-0130
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 879
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . peptides, cytokines, or components of the regulation of the cell cycle, or for the synthesis of regulative RNA molecules and **antisense** RNA, **ribozyme** or mRNA-editing-RNA. Furthermore, an important aspect of the invention is that the construction principle allows for the covalent linking of. . .

SUMM . . . non-tumor cells, such as antigen-presenting cells (macrophages, dendritic cells) Alternatively, genes which control the expression of peptide-presenting proteins, such as **CIITA** or ICSBP are of great importance.

SUMM . . . uptake of these complexes into the cytosol after endosomal uptake (Plank et.al., J.Biol.Chem. 269, 12918, (1994)). The covalent attachment of **antisense** desoxyoligonucleotides to haemagglutinine peptide is described by Bongartz et al. (Nuc.Acids Res. 22, 4681, 1994).

SUMM . . . peptides, cytokines, or components of the regulation of the cell cycle, or for the synthesis of regulative RNA-molecules, such as **antisense**-RNA, **ribozymes** or mRNA-editing RNA. Since the nucleic acid is covalently closed on both ends and no free hydroxyl-groups are available for. . .

SUMM . . . of advantage for the transcription of genes coding for RNA. Such promoter sequences can result in the expression of short **antisense**-RNAs, **ribozymes**, and artificial mRNA in vivo. RNA-polymerase III produces significantly more copies of RNA than polymerase II and has an exact. . .

SUMM . . . CD40, B7-1, and B7-2, proteins of the MHC-complexes I or II or .beta.-2 microglobulin, interferone consensus sequence binding protein ICSBP, **CIITA**, Flt3, or entire proteins or fragments thereof of presentable epitopes from tumor specific expressed mutated or non-mutated proteins, e.g. Ki-RAS-fragments,. . .

L3 ANSWER 6 OF 47 USPATFULL
ACCESSION NUMBER: 2003:78445 USPATFULL
TITLE: MHC class II antigen presenting cells containing oligonucleotides which inhibit Ii protein expression
INVENTOR(S): Xu, Minzhen, Northborough, MA, UNITED STATES
Qiu, Gang, Shewsbury, MA, UNITED STATES
Humphreys, Robert, Acton, MA, UNITED STATES
PATENT ASSIGNEE(S): Antigen Express, Inc., Worcester, MA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003054365	A1	20030320
APPLICATION INFO.:	US 2002-54387	A1	20020122 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-205995, filed on 4 Dec 1998, GRANTED, Pat. No. US 6368855 Continuation-in-part of Ser. No. US 1998-36746, filed on 9 Mar 1998, ABANDONED Continuation of Ser. No. US 1996-661627, filed on 11 Jun 1996, GRANTED, Pat. No. US 5726020
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kevin M. Farrell, Kevin M. Farrell, P.C., 18 York Street, P.O. Box 999, York Harbor, ME, 03911
NUMBER OF CLAIMS: 96
EXEMPLARY CLAIM: 1
LINE COUNT: 3050

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . decreasing expression) or by otherwise interfering with the Ii immunoregulatory function. Inhibition of Ii expression has been accomplished using various **antisense** technologies. An **antisense** oligonucleotide interacting with the AUG site of the mRNA for Ii protein has been described to decrease MHC class II. . . MHC class II molecules were not examined. More recently, Humphreys et al., U.S. Pat. No. 5,726,020 (1998) have identified three **antisense** oligonucleotides and a reverse gene construct which upon introduction into an antigen presenting cell expressing MHC class II molecules expressing. . .

SUMM . . . class includes copolymers comprised of nucleotide bases which hybridize specifically to the RNA molecule encoding mammalian Ii protein, for example **antisense** oligonucleotides, and also expressible reverse gene constructs which encode RNA molecules which hybridize specifically to the Ii RNA. In other. . .

SUMM . . . immune system. It has previously been shown that Ii protein expression in cells can be inhibited specifically and efficiently with **antisense** technology using specific oligonucleotides or reverse gene constructs. U.S. Pat. No. 5,726,020 (Humphreys et al.) exemplifies this previous work and. . .

SUMM . . . These copolymers contain nucleotide base sequences which are complementary to a targeted portion of the RNA molecule, otherwise known as **antisense** sequences. One example of such a copolymer is an **antisense** oligonucleotide. Copolymers inhibit protein translation from RNA by two mechanisms. One method is to block access to portions of the. . .

SUMM . . . where oligonucleotides and other copolymers hybridize are identified after gel electrophoresis of the RNA and autoradiography. Such experiments with Ii **antisense** oligonucleotides are presented in Example 1. The sites in the Ii RNA found in the present invention to be most. . .

SUMM . . . a sugar or phosphate group or both yet still can hybridize by Watson-Crick base pairs in the same way as **antisense** oligonucleotides and can be used for the same purposes. These copolymers containing nucleotide bases are functional equivalents of oligonucleotides in hybridizing to RNA. Summarized below are some of the modifications to oligonucleotides which change and improve their properties for **antisense** applications.

SUMM . . . arrangements of atoms that do not contain phosphorus and are uncharged (Sanghvi & Cook, Carbohydrates: synthetic methods and applications in **antisense** therapeutics. An overview. Chap. 1. In: Carbohydrate Modifications in **Antisense** Research. (:Sanghvi, Cook) (ACS Symposium Series, 580). American Chemical Society, Washington, D.C. 1-22 (1995); De Mesmaeker et al., Account. Chem.. . .

SUMM . . . (1994); De Mesmaeker et al., Account. Chem. Res. 28: 366-374 (1995); Sanghvi & Cook, Carbohydrates: synthetic methods and applications in **antisense** therapeutics. An overview. Chap. 1. In: Carbohydrate Modifications in **Antisense** Research. (:Sanghvi, Cook) (ACS Symposium Series, 580). American Chemical Society, Washington, D.C. 1-22 (1995); Freier & Altmann, Nucleic Acids Res.. .

SUMM . . . 8. Stereochemistry around the sugar ring is changed at the 1' position to give the a-nucleoside series (Lavignon et al., **Antisense** Research and Development 2: 315-324 (1992)), at the 2'-position to give the arabinose series, or at the 3'-position to give. . .

SUMM [0032] 12. The sugar is replaced by morpholine (Summerton et al., **Antisense** Nucleic Acid Drug D. 7: 63-70 (1997)).

SUMM . . . hybridized RNA molecule. Other chemical groups are so conjugated to catalyze cleavage of the hybridized RNA molecule (e.g. chelating agents). **Ribozymes** engineered into the copolymer also promote the cleavage of the Ii RNA. Another category of chemical groups that is conjugated. . .

SUMM [0071] The catalytically active sites from hammerhead and hairpin

ribozymes can be engineered into the copolymers to generate artificial **ribozymes** which catalyze the cleavage of the complementary Ii RNA (Santoro and Joyce, A general purpose RNA-cleaving DNA enzyme 94: 4262-4266 (1997)). In nature, a number of **ribozymes** play a role in site-specific cleavage of RNA during RNA processing. These can be broken into several types, including group I, group II, hammerhead, hairpin and HDV **ribozymes**, in addition to other less well characterized forms (Cech & Bass, Annu. Rev. Biochem. 55: 599-629 (1986)). The development of catalytically active **antisense** oligonucleotides has been reviewed by Christoffersen & Marr, J. Med. Chem. 38: 2023-2037 (1995). Alternatively, the same principles can be used to engineer **ribozymes** into reverse gene constructs, which are discussed in detail below.

SUMM [0083] 2. polylysine (Degols et al., **Antisense** Research and Development 2: 293-301 (1992))

SUMM [0084] 3. cholesterol and cholic acid (Chow et al., **Antisense** Research and Development 4: 81-86 (1994))

SUMM [0086] 1. liposomes (Zelphati & Szoka, Pharmaceut. Res. 13: 1367-1372 (1996); Juliano & Akhtar, **Antisense** Research and Development 2: 165-176 (1992))

SUMM [0088] 3. cyclodextrin (Zhao et al., **Antisense**. Res. Dev. 5: 185-192 (1995))

SUMM [0101] 3. cholesterol, cholic acid and a tetrapeptide, fMFLY, to target neutrophils (Chow et al., **Antisense** Research and Development 4: 81-86 (1994))

SUMM . . . J. Acq. Immun. Defic. Syndrome 7: 560-570 (1994)). This alteration impacts the biological properties of the copolymer (Chow et al., **Antisense** Research and Development 4: 81-86 (1994); Demirhan et al., Virus Genes 9: 113-119 (1995)). Another example is a copolymer conjugated. . .

SUMM . . . follow, several reverse gene constructs were designed and tested. Several of them were found to inhibit Ii protein expression in SaI/**CIITA** cells. Inhibition of Ii protein expression (up to 60% of cells) was observed in transfectants by some but not all. . .

SUMM . . . cells. When cells presenting proteins of the pathogen or elicited in response to the pathogen are appropriately contacted by an **antisense** reagent targeting the Ii protein, additional antigenic determinants are presented through the MHC class II molecules leading to expansion of. . . of therapeutic immunoglobulins. In this regard, only a portion of the virally infected cells need be treated with an Ii **antisense** therapeutic and reintroduced into the patient. Particularly in the case of Epstein-Barr virus infection of normal B cells, in which. . .

SUMM . . . only a portion of the pathogenic T cells, or a culture or clone thereof, needs be treated with an Ii **antisense** therapeutic and reintroduced into the patient.

SUMM . . . in cells lacking co-stimulatory signals, (e.g. cells without B7, or in which B7 expression is suppressed by treatment with B7 **antisense** constructs), will produce anergic responses.

SUMM . . . priming of the immune system to disease-specific or disease-related determinants. After such a priming event, the immune system, without additional **antisense** treatments, is capable of rejecting either the tumor or the pathogenic, autoreactive T cell. In contrast, in most current applications of **antisense** therapeutics for the control of disease (e.g. viral diseases such as HIV), upon discontinuing the **antisense** drug, the disease (or virus) rebounds. Another preferred value of this method, is that induction of an anti-disease priming of the immune response can be pursued with either in vivo or ex vivo use of the disclosed **antisense** compositions.

DETD Identification of Ii RNA Sites Hybridizing With **Antisense** Oligonucleotides

DETD . . . cleave RNA at sites which are hybridized to DNA was used to identify sites of Ii RNA which hybridized with **antisense** oligonucleotides. A series of deoxyoligonucleotides, each containing 18

bases in a sequence complementary, in a head-to-tail fashion, to a segment. . . of oligonucleotides, but lacking RNase H, or in the presence of a sense oligonucleotide control (SEQ ID NO:46) or an **antisense** oligonucleotide with one internal deletion (SEQ ID NO:43, SEQ ID NO:44 and SEQ ID NO:45). Oligonucleotide sequences yielding strongest cleavage were re-synthesized with phosphorothioate linkages for additional studies of **antisense** potency, presented in Examples 3, 4, and 5.

DETD . . . P31 mRNA, but similar procedures for analysis of hybridization sites are applicable to any species of RNA.

TABLE 1

Sequence of **Antisense** Phosphodiester Oligonucleotides Used in RNase H Mapping Experiment.

SEQ ID NO:	SEQUENCE	NUCLEOTIDE POSITION
5	5'-CAT GTT ATC CAT GGA CAT	318-301
6	5'-CAT GGA. . .	

DETD . . . bracket and was used in subsequent experiment shown in Table 4.

TABLE 2

RNase H mapping of accessible sites for mouse Ii **antisense** oligonucleotides.

OLIGONUCLEOTIDE	NUCLEOTIDE POSITION	Signal
SEQ ID NO: 5	318-301	-
SEQ ID NO: 6	309-292	+
SEQ ID NO:. . .		

DETD [0166] The **antisense** oligonucleotide sequence ID numbers, their nucleotide starting positions in Ii mRNA and intensity of products as judged on a scale. . .

DETD . . . yeast tRNA in 1.times. RNase H buffer, heated at 70.degree. C. for 3 minutes and cooled slowly to room temperature. **Antisense** oligodeoxynucleotide (0.2-1 pmol) was added and incubated at 37.degree. C. for 30 minutes, followed by adding 0.5 unit of E.. . .

DETD [0172] The study described here was performed with mouse SaI/**CIITA** cells but are applicable to any mammalian cell line.

DETD . . . electroporation of oligonucleotides into mammalian cells were tested to determine the conditions which produce maximal uptake with minimal cell damage. SaI/**CIITA** mouse sarcoma cells were subjected to electroporation using various combinations of voltage and capacitance. Fluorescein-labeled phosphorothioate oligonucleotide (SEQ ID NO:64). . .

DETD [0177] Phosphorothioate **antisense** oligonucleotide SEQ ID NO:64 (see Table 5) used in these studies was 5' labeled with fluorescein. It was synthesized and. . .

DETD [0179] The SaI/**CIITA** mouse sarcoma cell line was maintained in Iscove's Modified Dulbecco's Medium (IMDM, JRH Biosciences, Lenexa, Kans.) supplemented with 5% FCS. . .

DETD Specific Inhibition of Ii Expression in Cells by Phosphorothioate **Antisense** Oligonucleotides

DETD [0182] Optimal methods for **antisense** oligonucleotide incorporation, determined above, were used in an assay to determine the effect of Ii **antisense** oligonucleotides on Ii protein expression in a tumor cell line. The SaI/**CIITA** murine sarcoma cell line was used in these assays. These cells are stably transfected with a plasmid containing the gene for the MHC class II transcription activator factor **CIITA**, and express high levels of MHC class II and Ii proteins

DETD [0183] Thirteen sequences determined in Example 1 to strongly hybridized to murine Ii RNA were synthesized as phosphorothioate **antisense** oligonucleotides. These oligonucleotides were introduced into SaI/**CIITA** cells via electroporation. After incubation for 24 hours, cells were assayed for levels of Ii and MHC class II proteins. . . . Example 2. Suppression of expression of either Ii protein or MHC class II molecules was measured as the percentage of **antisense** oligonucleotide-treated cells showing the same intensity of fluorescence as control Ii-negative and MHC class II-negative cells (the parental SaI sarcoma cells without **CIITA** transfection). This measurement is cell-numbered in terms of reflecting the fraction of cells with complete suppression of the indicated protein. . .

DETD . . . class II protein expression was not affected in any of the cells, which demonstrates that the inhibition produced by the **antisense** oligonucleotides is specific for Ii expression.

DETD . . . recovery and viability of the cells. The best compound in the first splice donor region is SEQ ID NO:62. An **antisense** oligonucleotide (SEQ ID NO:64) complementary to polyadenylation site in 3' untranslated region also showed some activity.

TABLE 4

Inhibition of Ii but not I-E expression by phosphorothioate **antisense** oligonucleotides

Oligo SEQ ID NO:	Ii NEGATIVE CELLS % AVE.	SD	FOLD AVE.	SD	I-E NEGATIVE CELLS % AVE.	SD	FOLD AVE.	SD
NONE. . .								

DETD . . . well as the fold of the negative cells as compared with that of control cells treated in the absence of **antisense** oligonucleotide, from two independent experiments are reported.

TABLE 5

Antisense phosphorothioate oligonucleotides used to determine the most active compound at the sensitive sites. NUCLEOT

SEQ ID NO:	IDE POSITION	SEQUENCE
49		5'. . .

DETD [0187]

TABLE 6

Inhibition of Ii but not I-E expression by phosphorothioate **antisense** oligonucleotides II

A. Oligo SEQ ID NO:	Ii NEGATIVE CELLS % AVE.	SD	FOLD AVE.	SD	I-E NEGATIVE CELLS % AVE.	SD	FOLD AVE.. . .

DETD [0190] Phosphorothioate **antisense** oligonucleotides were synthesized and HPLC purified by Integrated DNA Technologies, Inc. (Coralville, Iowa).

DETD [0192] Electroporation of SaI/**CIITA** cells at 200 V and 1200 .mu.F, with individual oligonucleotides (50 .mu.M), was performed as described in Example 2. Cells. . .

DETD [0197] In this study, the most active **antisense** sequence identified in Example 3, SEQ ID NO:54 was used to compare relative potencies of various backbone modifications in inhibition. . . and (4) 2' methyloxyl modified phosphodiester (SEQ ID NO:67). 10 and 50 mM

each of the oligonucleotides were electroporated into SaI/**CIITA** sarcoma cells which were then cultured for 24 or 48 hours. Levels of inhibition in Ii protein expression as well. . .

DETD [0198]
TABLE 8

Inhibition of Ii expression by **antisense** oligonucleotides with differing backbone structures.

OLIGO SEQ ID NO:	Ii NEGATIVE CELLS 24	48	I-E NEGATIVE CELLS 24	48	VIABILITY 24	48
CONC.. . .						

DETD [0200] **Antisense** oligonucleotides, as listed in Table 7, were synthesized and HPLC-purified by Integrated DNA Technologies, Inc. (Coralville, Iowa). Electroporation, cell culture,. . .

DETD [0201] For these experiments, SaI sarcoma cells were first transfected with the gene for the **CIITA** transacting factor which up-regulates expression of MHC Class II molecules (Armstrong et al., Proc. Natl. Acad. Sci. USA 94: 6886 (1997)) to produce SaI/**CIITA** cells. Several Ii reverse gene constructs were made by inserting the DNA sequences listed in Table 9, which correspond to Ii mRNA sequences (coresponding sequence numbers are indicated), into expression vectors. The reverse gene constructs were then transfected into SaI/**CIITA** cells. Cells which had received the expression vectors were selected by growth in hygromycin containing medium. These cells were stained. . .

DETD . . . 5' UT to 1st exon (+)
Ii (-26, 97)

*Ii inhibition (up to about 60%) was observed (+) in screening of SaI/**CIITA** stable transfectants with these constructs.

DETD [0207] SaI/**CIITA** cells, the gift of Dr. Ostrand-Rosenberg, the University of Maryland, Baltimore, Md., were cultured in IMDM (JRH Biosciences, Lenexa, Kans.),. . .

DETD [0209] SaI/**CIITA** cells were transfected with mIi reverse gene constructs using lipofectin (GIBCO BRL) according to the manufacturer's instruction. Briefly, 10 .mu.l. . . 40 minutes. The two reactions were gently mixed together and incubated at room temperature for another 15 minutes. Meanwhile, 10.sup.5 SaI/**CIITA** cells were washed with Opt. MEM I and resuspended into 800 .mu.l of Opt. MEM I. The liposome/DNA reaction was gently dropped into the SaI/**CIITA** cells and then the cells were incubated at 37 C for 12-24 hours. The transfection medium was replace with 2. . .

DETD . . . from challenge with a parental tumor. For these experiments, SaI sarcoma cells were first transfected with the gene for the **CIITA** transacting factor which up-regulates expression of MHC Class II molecules (Armstrong et al., Proc. Natl. Acad. Sci. USA 94: 6886 (1997)) to produce SaI/**CIITA** cells. The transfected cells express both MHC class I and MHC class II molecules. Without transfection of the **CIITA** gene, the SaI cells express only MHC class I molecules. SaI/**CIITA** cells also express significant amounts of the Ii protein, along with the MHC class II molecules. Coexpression of Ii protein with MHC class II molecules occurs because the **CIITA** transacting factor also acts on genetic regulatory units upstream from (and within the first intron of) the structural gene for. . .

DETD [0213] The SaI/**CIITA** cells (expressing MHC Class I, MHC Class II molecules and the Ii protein) were treated with an **antisense** oligonucleotide directed to Ii mRNA (SEQ.ID.NO.:54) in order to suppress expression of the Ii protein. The degree of suppression of the Ii protein in the SaI/**CIITA** cells, and the lack of suppression of MHC Class II molecules was measured by methods presented above in Example 3. The **antisense** oligonucleotide compound SEQ.ID.NO.:54 profoundly suppressed Ii protein in about 35 percent of the SaI/**CIITA** cells, without significant effect upon the level

of expression of MHC Class II molecules. To prevent replication in the inoculated. . .

DETD . . . with SaI tumors at either 2.5.times.10.sup.5 cells/mouse, 7.5.times.10.sup.5 cells/mouse, and 20.times.10.sup.5 cells/mouse. Control mice which had been treated with fixed SaI/**CIITA** cells which had not been treated with a copolymer to suppress Ii, were also challenged with the above concentrations of. . . all control mice (C) with ascites tumor, had 1.5-2.5 ml ascites and were terminated. Among the mice which had received **CIITA** gene-transfected vaccine cells (AS mice), one mouse in the 2.5.times.10.sup.5 cells/mouse group and one mouse in the 7.5.times.10.sup.5 cells/mouse group,. . .

DETD . . . activity by actions of the helper T cells.

TABLE 11

Tumor incidence after challenge with SaI tumors,
in mice vaccinated with fixed, SaI/**CIITA** cells,
which had not been or had been treated with
compound SEQ. ID. NO.: 54.

2.5 .times. 10.sup.5 7.5 .times. 10.sup.5 20. . .

DETD . . . incidence of tumor ascites with a volume equal to or greater than 1.5 ml was scored in mice vaccinated with **CIITA** gene-transfected tumor cells which were treated with SEQ.ID.NO.:54 ("AS" for **antisense**, subgroups), or were not treated ("C" for control, subgroups).

DETD [0218] The **CIITA**-gene transfected SaI cells were incubated at 2.times.10.sup.6 cells/ml with 50 .mu.M compound SEQ.ID.NO.:54 and subjected to electroporation at 200 V,. . .

DETD . . . Vaccine cells were injected intraperitoneally into 15 mice at 2.5.times.10.sup.5 cells/mouse. A parallel group of fifteen mice were injected with SaI/**CIITA** cells which had not been treated with the SEQ.ID.NO.:54 copolymer.

DETD [0224] After 27 days, mice in three subgroups (5 mice per subgroup), of the mice which had been vaccinated with SaI/**CIITA** cells treated with SEQ.ID.NO:54, were challenged with SaI parental cells at three doses: 2.5.times.10.sup.5 cells, 7.5.times.10.sup.5 cells and 20.times.10.sup.5 cells, respectively. In parallel, three subgroups of mice vaccinated with fixed, SaI/**CIITA** cells which had not been treated with SEQ.ID.NO.:54, were challenged with SaI parental cells at the same three doses, respectively.. . .

DETD . . . induced in SaI cells after transfection of the gene for interferon gamma, rather than after transfection of the gene for **CIITA**. Second, viability of the vaccine cells was maintained by irradiation, while the malignant potential (ability to replicate) was destroyed.

DETD . . . scientific and economic reasons to prefer to induce MHC Class II molecules through the action of interferon gamma, rather than **CIITA**. For example, the action of interferon gamma might induce additional functions needed for optimal processing and presentation of tumor-related antigenic. . .

DETD . . . were prepared: 1) cells transfected with copolymer SEQ.ID.NO.:54 to suppresses Ii protein expression, and 2) cells which were not transfected. **CIITA** gene-transfected SaI cells were incubated at 2.times.10.sup.6 cells/ml with 50 .mu.M copolymer SEQ.ID.NO.:54 and electroporated at 200 V, 1200 .mu.fd. . .

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 1
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the Ii gene.
SEQUENCE: 1
ctcggtacct actgg

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 2
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 2
atccatggct ctagcctc 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 3
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 3
tctagcctct agtttttc 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 5
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 5
catgttatcc atggacat 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 6
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 6
catggacatt ggacgcat 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 7
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 7
tggacgcatc agcaaggg 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 8
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 8

cagcaaggga gtagccat
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 9
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 9 18
agtagccatc cgcatctg
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 10
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 10 18
ccgcatctgg ctcacagg
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 11
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 11 18
gctcacaggt ttggcaga
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 12
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 12 18
tttggcagat ttcggaag
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 13
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 13 18
tttcggaagc ttcatgcg
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 14
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 14
cttcatgcga aggctctc 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 15
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 15
aaggctctcc agttgcag 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 16
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 16
cagttgcagg ttctggga 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 17
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 17
gttctgggag gtgatggt 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 18
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 18
ggtgatggtc agcttgtc 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 19
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 19
cagcttgtct aggcggcc 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 20
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii

gene.
SEQUENCE: 20 18
taggcggccc tgttgctg
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 21
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 21 18
ctgttgctgg tacaggaa
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 22
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 22 18
gtacaggaag taagcagt
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 23
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 23 18
gtaagcagtg gtggcctg
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 24
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 24 18
ggtggcctgc ccagccaa
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 25
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 25 18
cccagccaag agcagagc
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 26
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense**

oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 26
gagcagagcc accaggac 18

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 27
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 27
caccaggaca gagacacc 18

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 28
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 28
agagacaccg gtgtacag 18

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 29
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 29
ggtgtacaga gctccacg 18

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 30
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 30
agctccacgg ctgcacct 18

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 31
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 31
gctgcacctt tctggctc 18

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 32
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:

OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 32

ttctggctct ctagggcg 18

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 33

LENGTH: 18

TYPE: DNA

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 33

tctagggcgg ttgcccag 18

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 34

LENGTH: 18

TYPE: DNA

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 34

gttgcccagt atgggcaa 18

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 35

LENGTH: 18

TYPE: DNA

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 35

tatgggcaac tgttcatg 18

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 36

LENGTH: 18

TYPE: DNA

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 36

ctgttcatgg ttagagat 18

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 37

LENGTH: 18

TYPE: DNA

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.

SEQUENCE: 37

gttagagatg aggtcgcg 18

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 38

LENGTH: 18

TYPE: DNA

ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene. 18

SEQUENCE: 38
gaggtcgcgt tggtcatc

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 39
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene. 18

SEQUENCE: 39
gcgttggtca tccatggc

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 40
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene. 18

SEQUENCE: 40
ttggtcatcc atggctct

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 41
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene. 18

SEQUENCE: 41
gtcatccatg gctctagc

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 42
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene. 18

SEQUENCE: 42
cacaggcgct gctgctgc

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 43
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene. 18

SEQUENCE: 43
atccatggct ctagccct

DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 44
LENGTH: 18
TYPE: DNA

ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 44 18
tctagcccta gtttttcc
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 45
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 45 18
agtttttccc acaggcgc
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 46
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 46 18
atggatgacc aacgcgac
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 47
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 47 18
ctagtttttc ccacaggc
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 48
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 48 18
ctgctgctgt tgctgctg
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 49
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 49 18
gtcgcgttgg tcatccat
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 50
LENGTH: 18

TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 50
tcgcgttggt catccatg 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 51
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 51
cgcgttggtc atccatgg 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 52
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 52
cgttggtcat ccatggct 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 53
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 53
gttggtcatc catggctc 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 54
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 54
tggtcatcca tggctcta 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 55
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 55
ggtcatccat ggctctag 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 56

LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 56
cacggctgca cctttctg 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 57
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 57
cggctgcacc tttctggc 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 58
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 58
tgcacctttc tggctctc 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 59
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 59
cacctttctg gctctcta 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 60
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 60
acctttctgg ctctctag 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 61
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 61
ctttctggct ctctaggg 18
DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 62
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 62
ctggctctct agggcggt 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 63
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 63
ggctctctag ggcggttg 18
DETD SEQUENCE CHARACTERISTICS:
SEQ ID NO: 64
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence **antisense** oligonucleotide corresponding to a specific region of the mouse Ii gene.
SEQUENCE: 64
gacaagcttg gctgagca 18
CLM What is claimed is:
28. The specific regulator of claim 6 which is a **ribozyme** designed to cleave the RNA molecule.

L3 ANSWER 7 OF 47 USPATFULL
ACCESSION NUMBER: 2003:70969 USPATFULL
TITLE: Modulating neuronal outgrowth via the major histocompatibility complex Class I (MHC I) molecule
INVENTOR(S): Kaufman, Daniel L., Los Angeles, CA, UNITED STATES
Hanssen, Lorraine, Los Angeles, CA, UNITED STATES
Zekzer, Dan, Encinitas, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003049254	A1	20030313
APPLICATION INFO.:	US 2002-161647	A1	20020605 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-295596P	20010605 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Sharon E. Crane, Ph.D., BURNS, DOANE, SWECKER & MATHIS, L.L.P., P.O. Box 1404, Alexandria, VA, 22313-1404
NUMBER OF CLAIMS: 66
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 2511
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0070] It has recently been determined that **CIITA** and RFX play a role in the regulation of Class I MHC expression. The implication of this determination is that. . .

SUMM . . . enhancer A and ISRE and mediates the constitutive and cytokine induced expression. The S-X-Y module is important to consitutive and **CIITA**-mediated transactivation. These modules are absent in antigen G expression. There may be some regulatory sequences in the proximal promoter region. . .

DETD [0111] "**Antisense**," as used herein, refers to the modulation of function of a target nucleic acid by compounds which specifically hybridize to it. **Antisense** compounds are commonly used as research reagents and diagnostics. For example, **antisense** oligonucleotides are often used by those of ordinary skill to determine the function of a particular gene because such oligonucleotides are able to inhibit gene expression with great specificity. **Antisense** oligonucleotides are also used as therapeutic moities in the treatment of disease states in mammals.

DETD [0181] In yet another embodiment, the composition may include a nucleic acid, for example an **antisense** molecule or **ribozyme**, which inhibits the expression of MHC I. Such a composition may be provided to the neurons either ex vivo or. . .

DETD [0258] The present invention extends to the preparation of **antisense** oligonucleotides and **ribozymes** that may be used to interfere with the expression of the MHC I at the translational level. This approach utilizes **antisense** nucleic acid and **ribozymes** to block translation of a specific mRNA, either by masking that mRNA with an **antisense** nucleic acid or cleaving it with a **ribozyme**.

DETD [0259] **Antisense** nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule.. . to that mRNA, forming a double stranded molecule. The cell does not translate an mRNA in this double-stranded form. Therefore, **antisense** nucleic acids interfere with the expression of mRNA into protein. Oligomers of about fifteen nucleotides and molecules that hybridize to. . . easy to synthesize and are likely to pose fewer problems than larger molecules when introducing them into MHC I-producing cells. **Antisense** methods have been used to inhibit the expression of many genes in vitro. Marcus-Sekura, 1988; Hambor et al., 1988.

DETD [0260] **Ribozymes** are RNA molecules possessing the ability to specifically cleave other single stranded RNA molecules in a manner somewhat analogous to DNA restriction endonucleases. **Ribozymes** were discovered from the observation that certain mRNAs have the ability to excise their own introns. By modifying the nucleotide. . .

DETD [0261] Investigators have identified two types of **ribozymes**, Tetrahymena-type and "hammerhead"-type. Hasselhoff and Gerlach, 1988. Tetrahymena-type **ribozymes** recognize four-base sequences, while "hammerhead"-type recognize eleven- to eighteen-base sequences. The longer the recognition sequence, the more likely it is to occur exclusively in the target mRNA species. Therefore, hammerhead-type **ribozymes** are preferable to Tetrahymena-type **ribozymes** for inactivating a specific mRNA species, and eighteen base recognition sequences are preferable to shorter recognition sequences.

DETD [0262] The DNA sequences described herein may thus be used to prepare **antisense** molecules against, and **ribozymes** that cleave mRNAs for MHC I and their ligands.

CLM What is claimed is:
23. The method of claim 22, wherein the agent is an **antisense** nucleic acid.

L3 ANSWER 8 OF 47 USPATFULL

ACCESSION NUMBER: 2003:44848 USPATFULL

TITLE: Method of modulating the efficiency of translation termination and degradation of aberrant mRNA involving a surveillance complex comprising human Upf1p,eucaryotic release factor 1 and eucaryotic release factor 3

INVENTOR(S):	Peltz, Stuart, Piscataway, NJ, UNITED STATES Czaplinski, Kevin, Somerset, NJ, UNITED STATES Weng, Youmin, Cranford, NJ, UNITED STATES
PATENT ASSIGNEE(S):	University of Medicine and Dentistry of New Jersey, New Brunswick, NY, UNITED STATES, 08903 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003032158	A1	20030213
APPLICATION INFO.:	US 2002-138784	A1	20020503 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-321649, filed on 28 May 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-86986P	19980528 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	PERKINS COIE LLP, POST OFFICE BOX 1208, SEATTLE, WA, 98111-1208
NUMBER OF CLAIMS:	28
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	11 Drawing Page(s)
LINE COUNT:	2935

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . a) providing a cell containing a vector comprising the nucleic acid encoding proteins of the complex, the complex; or an **antisense** molecule thereof; b) overexpressing said nucleic acid in said cell to produce an overexpressed complex so as to interfere with. . .

DETD . . . inhibit the decay pathway, stabilize nonsense transcripts or modulate the efficiency of translation termination are important for the success of **antisense** RNA technology. **Antisense** RNAs are small, diffusible, untranslated and highly structured transcripts that pair to specific target RNAs at regions of complementarity, thereby controlling target RNA function or expression. However, attempts to apply **antisense** RNA technology have met with limited success. The limiting factor appears to be in achieving sufficient concentrations of the **antisense** RNA in a cell to inhibit or reduce the expression of the target gene. It is likely that one impediment to achieving sufficient concentration is the nonsense decay pathway, since the short **antisense** RNA transcripts, which are not meant to encode a gene product, will likely lead to rapid translation termination if translation occurs, and consequently to rapid degradation and low abundance of the **antisense** RNA in the cell. Thus, the agents of the invention that stabilize aberrant mRNA transcripts may also stabilize **antisense** RNAs.

DETD [0066] This approach utilizes **antisense** nucleic acid and **ribozymes** to block translation of a specific mRNA, either by masking that mRNA with an **antisense** nucleic acid or cleaving it with a **ribozyme**.

DETD [0067] **Antisense** nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule. . . . to that mRNA, forming a double stranded molecule. The cell does not translate an mRNA in this double-stranded form. Therefore, **antisense** nucleic acids interfere with the expression of mRNA into protein. Oligomers of about fifteen nucleotides and molecules that hybridize to. . . are easy to synthesize and are likely to pose fewer problems than larger molecules when introducing them into organ cells. **Antisense** methods have been used to inhibit the expression of many genes in vitro (Marcus-Sekura, 1988, supra; Hambor et al., 1988,. . .

DETD [0068] **Ribozymes** are RNA molecules possessing the ability to specifically cleave other single stranded RNA molecules in a manner somewhat analogous to DNA restriction endonucleases. **Ribozymes**

were discovered from the observation that certain mRNAs have the ability to excise their own introns. By modifying the nucleotide. . .

DETD [0069] Investigators have identified two types of **ribozymes**, Tetrahymena-type and "hammerhead"-type. Tetrahymena-type **ribozymes** recognize four-base sequences, while "hammerhead"-type recognize eleven- to eighteen-base sequences. The longer the recognition sequence, the more likely it is to occur exclusively in the target mRNA species. Therefore, hammerhead-type **ribozymes** are preferable to Tetrahymena-type **ribozymes** for inactivating a specific mRNA species, and eighteen base recognition sequences are preferable to shorter recognition sequences.

DETD . . . cell, said method comprising: a) providing a cell containing a vector comprising the nucleic acid encoding the complex; or an **antisense** thereof; b) overexpressing said nucleic acid vector in said cell to produce an overexpressed complex so as to interfere or. . .

DETD . . . POTASSIUM CHANNEL, INWARDLY-RECTIFYING, SUBFAMILY J, MEMBER 1, PLAKOPHILIN 1, PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE ISOFORM 1B, ALPHA SUBUNIT, PLECTIN 1, SHORT STATURE, **MHC CLASS II TRANSACTIVATOR**, HYPOPHOSPHATEMIA, VITAMIN D-RESISTANT RICKETS, RIEG BICOID-RELATED HOMEOBOX TRANSCRIPTION FACTOR 1, MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2E, RETINITIS PIGMENTOSA-3, MutS, E. COLI,. . .

DETD . . . and/or degradation of aberrant transcripts in a cell in a cell, said method comprising: a) providing a cell; b) expressing **antisense** transcript of the complex in sufficient amount to bind to the complex.

DETD [0099] In one embodiment, a nucleic acid encoding the complex or factors of the complex; an **antisense** or **ribozyme** specific for the complex, or specific for regions of the release factors and Upf1p, are introduced in vivo in a. . .

DETD . . . invention provides for co-expression of a gene product that modulates activity at the peptidyl transferase center and a therapeutic heterologous **antisense** or **ribozyme** gene under control of the specific DNA recognition sequence by providing a gene therapy expression vector comprising both a gene. . . peptidyl transferase center (including but not limited to a gene for a mutant frameshift or mRNA decay protein, or an **antisense** RNA or **ribozyme** specific for mRNA encoding such a protein) with a gene for an unrelated **antisense** nucleic acid or **ribozyme** under coordinated expression control. In one embodiment, these elements are provided on separate vectors; alternatively these elements may be provided. . .

CLM What is claimed is:

13. The agent of claim 6, wherein the agent is an **antisense** molecule or a **ribozyme**.

24. A method of modulating the efficiency of translation termination of mRNA and/or degradation of abberant transcripts in a cell,. . . providing a cell containing a vector comprising the nucleic acid encoding the complex of claims 1 or 2; or an **antisense** thereof; b) overexpressing said vector in said cell to produce an overexpressed complex so as to interfere with the function. . .

L3 ANSWER 9 OF 47 USPATFULL

ACCESSION NUMBER: 2003:44371 USPATFULL

TITLE: Combined growth factor-deleted and thymidine kinase-deleted vaccinia virus vector

INVENTOR(S): McCart, J. Andrea, Toronto, CANADA
Bartlett, David L., Pittsburgh, PA, UNITED STATES
Moss, Bernard, Bethesda, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003031681	A1	20030213

APPLICATION INFO.: US 2001-991721 A1 20011113 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	WO 2000-US14679	20000526
	US 1999-137126P	19990528 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KNOBBE MARTENS OLSON & BEAR LLP, 2040 MAIN STREET, FOURTEENTH FLOOR, IRVINE, CA, 91614
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 2762
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . in vivo. Whole genes, open reading frames (ORFs), and other exogenous nucleotide fragments, such as nucleic acid sequences to generate **antisense** products, are contemplated for expression using the vaccinia virus vectors of the present invention.

DETD . . . bubr1, bwr1a, bwr1b, bws, bwscr1a, bwscr1b, bzrp, bzx, c11orf13, c1nh, c1qa, c1qb, c1qbp, c1qg, c1r, c1s, c2, c21orf1, c21orf2, c21orf3, **c2ta**, c3, c3br, c3dr, c3g, c4a, c4b, c4bpa, c4bpb, c4f, c4s, c5, c5ar, c5r1, c6, c7, c8a, c8b, c8g, c9, ca1,. . .

DETD . . . mga, mga1, mga3, mgat1, mgat2, mgat5, mgc1, mgcn, mgcr, mgct, mgdf, mgea, mgf, mgi, mgmt, mgp, mgsa, mgst1, mgst2, mhc, **mhc2ta**, mhp2, mhs, mhs2, mhs3, mhs4, mhs6, mia, mic10, mic11, mic12, mic17, mic18, mic2, mic2x, mic2y, mic3, mic4, mic7, mica, micb,. . .

DETD . . . Briefly, 1 .mu.l of isolated DNA and 1.mu.l of each primer (TK sense primer: 5'-GATCTTCTATCTCGGTTTCCTCAC-3' (SEQ ID NO. 1); TK **antisense** TK **antisense** primer: 5'-GATCGATAATAGATACGGAACGGG-3' (SEQ ID NO. 2); VGF sense primer: 5'-CTGATGTTGTTGTTCGTCGC-3' (SEQ ID NO. 3), VGF **antisense** primer: 5'-GGTAGTTTAGTTCGTCGAGTGAACC-3' (SEQ ID NO. 4))) were added to 47 ul of PCR Supermix (Gibco BRL, Gaithersberg, Md.). 25 cycles,. . .

DETD . . . the insertion of the multiple cloning site (MCS) of pBluescript KS II (+) (Stratagene; La Jolla, Calif.). To prevent possible **antisense** transcripts driven by the native vaccinia thymidine kinase promoter, two primers are designed to encode an early termination signal (TTTTTNT). . . virus p7.5 early/late and a synthetic early/late promoter, as described in Chakrabarti, et al., BioTechniques 23:1094-1097 (1997), in sense and **antisense** direction is inserted immediately upstream so that the gpt-gene is under control of the p7.5 promoter. A gene of interest,. . .

L3 ANSWER 10 OF 47 USPATFULL
ACCESSION NUMBER: 2003:74268 USPATFULL
TITLE: Method for identifying a compound to be tested for an ability to reduce immune rejection by determining Stat4 and Stat6 proteins
INVENTOR(S): Hancock, Wayne William, Medfield, MA, United States
Ozkaynak, Engin, Milford, MA, United States
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6534277	B1	20030318
APPLICATION INFO.:	US 2001-972800		20011005 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-549654, filed on 14 Apr 2000, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Kemmerer, Elizabeth
ASSISTANT EXAMINER: Li, Ruixiang
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP

NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 69 Drawing Figure(s); 64 Drawing Page(s)
LINE COUNT: 7647
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . Stat 1-responsive promoter are well known, and include, for example GBP-1, inducible NO synthase (iNOS), ICAM, IRF-1, major histocompatibility complex (**MHC**) **class II transactivator** (**CIITA**). See, e.g., Lew et al., 1991, Mol. Cell. Biol. 11:182-191, Gao et al., 1997, J. Biol. Chem. 272:1226-1230, Caldenhoven et. . .

DETD First, such compounds can include, for example, **antisense**, **ribozyme**, or triple helix compounds that can downregulate the expression or Stat1, Stat2, Stat3, Stat4, SOCS1 or SOCS3. Such compounds are. . .

DETD In specific embodiments, Stat1 **antisense** oligonucleotides, Stat2 **antisense** oligonucleotides, Stat3 **antisense** oligonucleotides, or any combination thereof, are administered to reduce immune rejection. In other embodiments one or more anti-Stat1 antibodies, anti-Stat2. . .

DETD . . . peptides that compete with Jak2 for binding to the IL-12R.beta..sub.2 can be utilized. In other embodiments, such compounds include Jak2 **antisense** molecules, triple helix molecules or **ribozyme** molecules that serve to downregulate the expression of Jak2. Representative **antisense** compositions are described in detail below. Such compounds also include antibodies or fragments thereof that specifically bind to and inhibit. . .

DETD . . . one or more peptides that compete with Tyk2 for binding to the IL-12R.beta..sub.1. In other embodiments, such compounds include Tyk2 **antisense** molecules, triple helix molecules or **ribozyme** molecules that serve to downregulate the expression of Tyk2. Representative **antisense** compositions are described in detail below.

DETD **ANTISENSE**, **RIBOZYME**, TRIPLE-HELIX COMPOSITIONS

DETD Representative, non-limiting examples of Stat1 **antisense** molecules include the following: 5'-GCT GAA GCT CGA ACC ACT GTG ACA TCC-3' (SEQ ID NO:19); and 5'-AAG TTC GTA. . .

DETD Representative, non-limiting examples of Stat2 **antisense** molecules include the following: 5'-CAT CTC CCA CTG CGC CAT TTG GAC TCT TCA -3' (SEQ ID NO:21); and 5'-CAG. . .

DETD Representative, non-limiting examples of Stat3 **antisense** molecules include the following: 5'-CTG GTT CCA CTG AGC CAT CCT GCT GCA TCAG-3' (SEQ ID NO:23); and 5'-CTG TAG. . .

DETD Representative, non-limiting examples of Stat4 **antisense** molecules include the following: 5'-GAT TCC ACT GAG ACA TGC TGC TCT CTC TCT C-3' (SEQ ID NO:25); and 5'-GAC. . .

DETD Representative, non-limiting examples of Jak2 **antisense** molecules include the following: 5'-GCC AGG CCA TTC CCA TCT AGA GCT TTT TTC-3' (SEQ ID NO:27); and 5'-CGT AAG. . .

DETD Representative, non-limiting examples of Tyk2 **antisense** molecules include the following: 5'-CCC ACA CAG AGG CAT GGT CCC CAC CAT TCA-3' (SEQ ID NO:29); and 5'-GGC CAT. . .

DETD Representative, non-limiting examples of SOCS1 **antisense** molecules include the following: 5'-CCT GGT TGC GTG CTA CCA TCC TAC TCG AGG GGC-3' (SEQ ID NO:31); and 5'-CAC. . .

DETD Representative, non-limiting examples of SOCS3 **antisense** molecules include the following: 5'-GCT GTG GGT GAC CAT GGC GCA CGG AGC CAG CG-3' (SEQ ID NO:33); and 5'-GGC. . .

DETD In addition, standard techniques can be utilized to produce **antisense**, triple helix, or **ribozyme** molecules for use as part of the methods described herein. First, standard techniques can be utilized for the production of **antisense** nucleic acid molecules, i.e., molecules which are complementary to a sense nucleic acid encoding a polypeptide of interest (e.g., Stat1,. . . SOCS3), e.g., complementary to the coding strand of a double-stranded cDNA

molecule or complementary to an mRNA sequence. Accordingly, an **antisense** nucleic acid can hydrogen bond to a sense nucleic acid. The **antisense** nucleic acid can be complementary to an entire coding strand, or to only a portion thereof, e.g., all or part of the protein coding region (or open reading frame). An **antisense** nucleic acid molecule can be **antisense** to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a polypeptide of. . .

DETD An **antisense** oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides or more in length. An **antisense** nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an **antisense** nucleic acid (e.g., an **antisense** oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the **antisense** and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the **antisense** nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine,. . . queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the **antisense** nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an **antisense** orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an **antisense** orientation to a target nucleic acid of interest).

DETD **Antisense** nucleic acid molecules administered to a subject or generated in situ such that they hybridize with or bind to cellular. . . hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an **antisense** nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of **antisense** nucleic acid molecules of the invention includes direct injection at a tissue, e.g., transplant or autoimmune lesion, site. Alternatively, **antisense** nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, **antisense** molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell, e.g., T cell, surface, e.g., by linking the **antisense** nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The **antisense** nucleic acid molecules can also be delivered to cells using vectors, e.g., gene therapy vectors, described below. To achieve sufficient intracellular concentrations of the **antisense** molecules, vector constructs in which the **antisense** nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

DETD An **antisense** nucleic acid molecule of interest can be an .alpha.-anomeric nucleic acid molecule. An a-anomeric nucleic acid molecule forms specific double-stranded. . . to the usual .beta.-units, the strands run parallel to each other (Gaultier et al. (1987) Nucleic Acids Res. 15:6625-6641). The **antisense** nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue et al. (1987) Nucleic Acids Res. 15:6131-6148) or a chimeric RNA-DNA. . .

DETD **Ribozymes** are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid,

such as an mRNA, to which they have a complementary region, and can also be generated using standard techniques. Thus, **ribozymes** (e.g., hammerhead **ribozymes** (described in Haselhoff and Gerlach (1988) Nature 334:585-591)) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A **ribozyme** having specificity for a nucleic acid molecule encoding a polypeptide of interest can be designed based upon the nucleotide sequence. . .

DETD In one embodiment, Stat4 **antisense** oligonucleotides are administered to reduce immune rejection by way of gene therapy. In another embodiment, nucleic acid molecules comprising sequences. . .

DETD In specific embodiments, Stat1 **antisense** oligonucleotides, Stat2 **antisense** oligonucleotides, Stat3 **antisense** oligonucleotides, or the combination thereof are administered to reduce immune rejection by way of gene therapy. In other embodiments, nucleic. . .

DETD In one embodiment, viral vectors that contain Stat4 **antisense** oligonucleotides are used (see Miller et al., 1993, Meth. Enzymol. 217:581-599). In another embodiment, viral vectors that contain nucleic acids. . .

DETD . . . Gln Ala Pro Ser Val Phe
1170 1175 1180
Ser Val Cys
1185

SEQUENCE CHARACTERISTICS:
SEQ ID NO: 19
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 19
gctgaagctc gaaccactgt gacatcc 27

SEQUENCE CHARACTERISTICS:
SEQ ID NO: 20
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 20
aagttcgtac cactgagaca tcctgcc 27

SEQUENCE CHARACTERISTICS:
SEQ ID NO: 21
LENGTH: 30
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 21
catctcccac tgcgccattt ggactcttca 30

SEQUENCE CHARACTERISTICS:
SEQ ID NO: 22
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 22
cagcatttcc cactgcgcca tttgggc 27

SEQUENCE CHARACTERISTICS:
SEQ ID NO: 23
LENGTH: 31
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 23
ctggttccac tgagccatcc tgctgcatca g 31
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 24
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 24
ctgtagctga ttccattggg ccatcct 27
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 25
LENGTH: 31
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 25
gattccactg agacatgctg ctctctctct c 31
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 26
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 26
gacttgattc cactgagaca tgctagc 27
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 27
LENGTH: 30
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 27
gccaggccat tcccatctag agctttttc 30
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 28
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 28
cgtaaggcag gccattccca tgcagag 27
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 29
LENGTH: 30
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 29
cccacacaga ggcatggtcc ccaccattca 30
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 30
LENGTH: 33
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule

SEQUENCE: 30
ggccatcccc cagtggcgca gaggcatgct ccc 33
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 31
LENGTH: 33
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 31
cctggttgcg tgctaccatc ctactcgagg ggc 33
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 32
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 32
cacctggttg tgtgctacca tcctact 27
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 33
LENGTH: 32
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 33
gctgtgggtg accatggcgc acggagccag cg 32
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 34
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: **antisense** molecule
SEQUENCE: 34
ggcgggaaac ttgctgtggg tgaccat 27
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 35
LENGTH: 22
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: primer
SEQUENCE: 35
gaactttcag ctgttacttt cc 22
SEQUENCE CHARACTERISTICS:
SEQ. . .

L3 ANSWER 11 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:388421 CAPLUS
TITLE: Radiation Improves Intratumoral Gene Therapy for Induction of Cancer Vaccine in Murine Prostate Carcinoma
AUTHOR(S): Hillman, Gilda G.; Xu, Minzhen; Wang, Yu; Wright, Jennifer L.; Lu, Xueqing; Kallinteris, Nikoletta L.; Tekyi-Mensah, Samuel; Thompson, Timothy C.; Mitchell, Malcolm S.; Forman, Jeffrey D.
CORPORATE SOURCE: Department of Radiation Oncology, Barbara Ann Karmanos Cancer Institute at Wayne State University School of Medicine and Harper Hospital, Detroit, MI, 48201, USA
SOURCE: Human Gene Therapy (2003), 14(8), 763-775
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Our goal was to convert murine RM-9 prostate carcinoma cells in vivo into antigen-presenting cells capable of presenting endogenous tumor antigens and triggering a potent T-helper cell-mediated immune response essential for the generation of a specific antitumor response. We showed that generating the major histocompatibility complex (MHC) class I+/class II+/Ii- phenotype, within an established s.c. RM-9 tumor nodule, led to an effective immune response limiting tumor growth. This phenotype was created by intratumoral injection of plasmid cDNAs coding for interferon gamma, **MHC class II transactivator** , and an **antisense** reverse gene construct (RGC) for a segment of the gene for Ii protein (-92,97). While this protocol led to significant suppression of tumor growth, there were no disease-free survivors. Nevertheless, irradn. of the tumor nodule on the day preceding initiation of gene therapy yielded 7 of 16 mice that were disease-free in a long-term follow up of 57 days compared to 1 of 7 mice receiving radiotherapy alone. Mice receiving radiotherapy and gene therapy rejected challenge with parental RM-9 cells and demonstrated specific cytotoxic T-cell activity in their splenocytes but not the mouse cured by radiation alone. These data were reproduced in addnl. expts. and confirmed that tumor irradn. prior to gene therapy resulted in complete tumor regression and specific tumor immunity in more than 50% of the mice. Increasing the no. of plasmid injections after tumor irradn. induced tumor regression in 70% of the mice. Administering radiation before this novel gene therapy approach, that creates an in situ tumor vaccine, holds promise for the treatment of human prostate carcinoma.

L3 ANSWER 12 OF 47 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:271955 CAPLUS
DOCUMENT NUMBER: 136:308521
TITLE: **Antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression
INVENTOR(S): Xu, Minzhen; Qiu, Gang; Humphreys, Robert
PATENT ASSIGNEE(S): Antigen Express, Inc., USA
SOURCE: U.S., 36 pp., Cont.-in-part of U.S. Ser. No. 36,746, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6368855	B1	20020409	US 1998-205995	19981204
US 5726020	A	19980310	US 1996-661627	19960611
WO 2000034467	A1	20000615	WO 1999-US28096	19991124
W: AU, CA, CN, JP, KR				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1135482	A1	20010926	EP 1999-961831	19991124
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002531582	T2	20020924	JP 2000-586901	19991124
US 2003054365	A1	20030320	US 2002-54387	20020122

PRIORITY APPLN. INFO.:
US 1996-661627 A1 19960611
US 1998-36746 B2 19980309
US 1998-205995 A 19981204
WO 1999-US28096 W 19991124

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression

AB Disclosed is a specific regulator of Ii protein (class II antigen invariant chain) gene expression or immunoregulatory function. Specifically disclosed are several forms of the specific regulator of Ii, including those which function through the formation of a duplex mol. with an RNA mol. encoding mammalian Ii protein to inhibit Ii protein synthesis at the translation level. This class includes copolymers comprised of nucleotide bases which hybridize specifically to the RNA mol. encoding mammalian Ii protein, and also expressible reverse gene constructs. In other aspects, the disclosure relates to MHC class II-pos. antigen presenting cells contg. a specific regulator of Ii expression. Such cells are useful, for example, in the display of autodeterminant peptides in assocn. with MHC class II proteins. Compns. of the invention find application in methods for treating diseases, for example malignancies and autoimmune disorders, in a patient by enhancing immunol. attack on undesired cells. An addnl. application is the isolation of autodeterminant peptides from a cell. RNAse H mapping was used to identify sites on the Ii mRNA that are accessible to **antisense** oligonucleotides. Use of phosphorothioate oligonucleotides is demonstrated in vitro. The most effective of the **antisense** oligonucleotides was used to inhibit Ii gene expression in the sarcoma cell line SaI in which MHCII antigen gene expressed was increased by overexpression of the **CIITA** gene. Formaldehyde fixed Ii-deficient cells were used to inoculate mice. Mice challenged with 20.times.105 SaI cells did not develop tumors.

ST Ii antigen **antisense** DNA MHCII presenting cell; sarcoma Ii antigen **antisense** DNA; cancer vaccine Ii antigen **antisense** DNA

IT Protein motifs
(CLIP, **antisense** DNA binding to region encoding; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT **Antisense** oligonucleotides
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Ii gene; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MHC (major histocompatibility complex), class II; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Oligonucleotides
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(analogs, **antisense**; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT RNA splicing
(**antisense** inhibition of; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Antigen-presenting cell
(**antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Invariant chain (class II antigen)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Antitumor agents
(**antisense** oligonucleotides to Ii gene as; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Phosphorothioate oligonucleotides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antisense**; **antisense** oligonucleotides for MHC

class II antigen presenting cells for inhibition of Ii protein expression)

IT Genetic element
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(exon, Ii gene, **antisense** DNA inhibiting splicing of; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT **Antisense** DNA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for Ii antigen gene; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for Ii antigen, **antisense** inhibition of expression of; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT **Ribozymes**
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibiting expression of Ii gene expression; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Genetic element
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intron, Ii gene, **antisense** DNA inhibiting splicing of; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Codons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(termination, Ii gene, **antisense** nucleic acids binding to; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Vaccines
(tumor, tumor cells with Ii gene expression inhibited for use in; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT Antitumor agents
(vaccines, tumor cells with Ii gene expression inhibited for use in; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT 409411-07-0 409411-08-1 409411-09-2 409411-10-5 409411-11-6 409411-12-7 409411-13-8 409411-14-9 409411-15-0 409411-16-1, 64: PN: US6368855 SEQID: 68 claimed DNA 409411-17-2, 67: PN: US6368855 SEQID: 71 claimed DNA 409411-18-3, 68: PN: US6368855 SEQID: 72 claimed DNA 409411-19-4, 71: PN: US6368855 SEQID: 75 claimed DNA 409411-20-7, 73: PN: US6368855 SEQID: 77 claimed DNA 409411-21-8, 74: PN: US6368855 SEQID: 78 claimed DNA 409411-22-9, 75: PN: US6368855 SEQID: 79 claimed DNA
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antisense** oligonucleotide to Ii gene; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT 1904-98-9, 2,6-Diaminopurine 134700-29-1, 5-Propynyluracil 151091-68-8, 5-Propynylcytosine
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antisense** oligonucleotides contg.; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT 409411-23-0

RL: PRP (Properties)
(nucleotide sequence; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

IT 409411-59-2 409411-60-5 409411-61-6 409411-62-7 409411-63-8
409411-64-9 409411-65-0 409411-66-1 409411-67-2 409411-68-3
409411-69-4 409411-70-7 409411-71-8 409411-72-9 409411-73-0
409411-74-1 409411-75-2 409411-76-3 409411-77-4 409411-78-5
409411-79-6 409411-80-9 409411-81-0 409411-82-1 409411-83-2
409411-84-3 409411-85-4 409411-86-5 409411-87-6 409411-88-7
409411-89-8 409411-90-1 409411-91-2 409411-92-3 409411-93-4
409411-94-5 409411-95-6 409411-96-7 409411-97-8 409411-98-9
409411-99-0 409412-00-6 409412-01-7 409412-02-8 409412-03-9
409412-04-0 409412-05-1 409412-06-2 409412-07-3 409412-08-4
409412-09-5 409412-10-8 409412-11-9 409412-12-0 409412-13-1
409412-14-2 409412-15-3 409412-16-4

RL: PRP (Properties)
(unclaimed nucleotide sequence; **antisense** oligonucleotides for MHC class II antigen presenting cells for inhibition of Ii protein expression)

L3 ANSWER 13 OF 47 USPATFULL
ACCESSION NUMBER: 2002:294261 USPATFULL
TITLE: TNF and IFN stimulated genes and uses therefor
INVENTOR(S): Wong, Grace, Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164299	A1	20021107
APPLICATION INFO.:	US 2001-854432	A1	20010511 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-203624P	20000512 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Dike, Bronstein, Roberts & Cushman, Intellectual Property Patent Practice, EDWARDS & ANGELL, LLP, 130 Water Street, Boston, MA, 02109
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
LINE COUNT: 1720
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0097] Further, **antisense** and **ribozyme** molecules that inhibit expression of the target gene can also be used in accordance with the invention to reduce the. . .

SUMM . . . compounds that can be used to reduce or inhibit either wild type, or if appropriate, mutant target gene activity are **antisense**, **ribozyme**, and triple helix molecules. Techniques for the production and use of such molecules are well known to those of skill. . .

SUMM . . . act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. With respect to **antisense** DNA, oligodeoxyribonucleotides derived from the translation initiation site, e.g., between the -10 and +10 regions of the target gene nucleotide. . .

SUMM [0100] **Ribozymes** are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. (For a review, see, for example, Rossi, 1994, Current Biology 4:469-471.) The mechanism of **ribozyme** action involves sequence specific hybridization of the **ribozyme** molecule to complementary target RNA, followed by a endonucleolytic cleavage. The composition of **ribozyme** molecules must include one or more sequences complementary to the target gene mRNA and must include the well-known catalytic sequence. . . is incorporated by reference herein in its entirety. As such within the

scope of the invention are engineered hammerhead motif **ribozyme** molecules that specifically and efficiently catalyze endonucleolytic cleavage of RNA sequences encoding target gene proteins.

SUMM [0101] Specific **ribozyme** cleavage sites within any potential RNA target are initially identified by scanning the molecule of interest for **ribozyme** cleavage sites that include the following sequences, GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and. . .

SUMM [0102] Nucleic acid molecules to be used in **triplex** helix formation for the inhibition of transcription should be single stranded and composed of deoxynucleotides. The base composition of these. . . are located on a single strand of the targeted duplex, resulting in GGC triplets across the three strands in the **triplex**. Alternatively, the potential sequences that can be targeted for triple helix formation can be increased by creating a so called. . .

SUMM [0103] In instances wherein the **antisense**, **ribozyme**, and/or triple helix molecules described herein are utilized to reduce or inhibit mutant gene expression, it is possible that the technique utilized can also efficiently reduce or inhibit the transcription (triple helix) and/or translation (**antisense**, **ribozyme**) of mRNA produced by normal target gene alleles such that the possibility can arise wherein the concentration of normal target. . .

SUMM [0104] Anti-sense RNA and DNA, **ribozyme** and triple helix molecules of the invention can be prepared by any method known in the art for the synthesis. . . chemical synthesis. Alternatively, RNA molecules can be generated by in vitro and in vivo transcription of DNA sequences encoding the **antisense** RNA molecule. Such DNA sequences can be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, **antisense** cDNA constructs that synthesize **antisense** RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines.

DETD . . . AA024028.1

2 162 317 Mus musculus CIPER protein (Ciper) mRNA, complete cds {IMAGE:355 W47752.1

2.1 64 137 Mus musculus classII MHC transactivator **CIITA** mRNA, complete cds {I AA178010.1

2.1 400 836 Mus musculus G-protein-like LRG-47 mRNA, complete cds {IMAGE:651 AA214784.1

2.1 36 74 Mus musculus. . .

L3 ANSWER 14 OF 47 USPATFULL

ACCESSION NUMBER: 2002:280808 USPATFULL

TITLE: Transcription factor of MHC class II genes, substances capable of inhibiting this new transcription factor and medical uses of these substances

INVENTOR(S): Masternak, Krzysztof, Morges, SWITZERLAND
Reith, Walter, Carouge, SWITZERLAND
Mach, Bernard, Pregny-Chambesy, SWITZERLAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002156258	A1	20021024
APPLICATION INFO.:	US 2001-840243	A1	20010424 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 1999-EP8026, filed on 22 Oct 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	EP 1998-120085	19981024

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SUMM . . . The invention also relates to a novel protein complex comprising this new transcription factor and other transcription factors, together with **CIITA**, and to methods of identifying inhibitors capable of inhibiting the formation of the complex.

SUMM . . . reflects the existence of four essential regulators of MHC-II expression.sup.2. The regulatory genes that are defective in complementation groups A (**MHC2TA**), C (RFX5) and D (RFXAP) have been identified.sup.8-10. **CIITA** (**MHC2TA** gene product) is a non DNA binding co-activator, whose expression controls the cell type specificity and inducibility of MHC-II genes.sup.8,. . .

SUMM . . . an additional subunit of RFX. However, neither complementation of defective cells, an approach that had led to the cloning of **MHC2TA** (ref.8) and RFX5 (ref.9) genes, nor classical affinity purification of the RFX complex, which had allowed the cloning of RFXAP. . .

SUMM . . . a variety of strategies. These have included functional complementation assays similar to those that had led to the discovery of **CIITA** (ref.8) and RFX5 (ref.9), classical multistep purification, as was used in the identification of RFXAP (ref.10), mutagenesis by retroviral insertion,. . .

SUMM . . . such as the cooperative interactions that stabilize the higher order RFX-X2BP-NF-Y complex or direct contacts between RFX and the co-activator **CIITA**.

SUMM . . . the corresponding ESTs (over 80 different clones) have been isolated from a wide variety of different tissues. The gene encoding **CIITA** (**MHC2TA**), on the other hand, is extremely tightly regulated, with a constitutive expression that is restricted to professional antigen presenting cells. It is the expression of **CIITA**, either constitutive in certain specialized cells or inducible in others, that determines activation of MHC-II promoters.sup.11, 12. Thus, two distinct regulatory components, the ubiquitously expressed RFX complex and the highly regulated transactivator **CIITA**, must act in concert.

SUMM . . . First, patients from the different genetic complementation groups have indistinguishable clinical features.sup.2-4. Thus, defects in four distinct and unrelated genes (**MHC2TA**, RFX5, RFXAP and RFXANK) all result in a single disease having a remarkably homogeneous clinical and biological phenotype. Second, the. . . of both constitutive and inducible expression of MHC-II genes in all cell types.sup.2-4. This indicates that all four trans-activating factors (**CIITA**, RFX5, RFXAP and RFXANK) are dedicated to the control of MHC-II genes. This restriction in specificity is also uncommon.

SUMM . . . remarkably stable higher-order nucleoprotein complex (enhanceosome). Enhanceosome assembly is essential but not sufficient for MHC-II transcription. This ultimately depends on **CIITA**, a highly regulated and gene specific factor that governs all spatial, temporal and quantitative aspects of MHC-II expression. **CIITA** was first identified as a factor that is mutated in MHC-II deficiency, a hereditary disease of gene regulation characterized by. . . MHC-II expression. Despite extensive studies, its mode of action has remained unclear. Here we show for the first time that **CIITA** is physically recruited to MHC-II promoters, by a mechanism implicating multiple protein-protein interactions with the enhanceosome. **CIITA** thus represents a paradigm for a novel type of gene-specific and highly regulated transcriptional co-activator. **CIITA** is a master control factor determining the cell type specificity, induction and level of MHC-II expression. It thus represents a. . . the regulation of adaptive immune responses. Despite the widespread interest this has evoked, surprisingly little has been learned on how **CIITA** actually exerts its control over

MHC-II genes. It has been postulated to activate transcription via putative N-terminal acidic and proline/serine/threonine/ rich activation domains capable of contacting components of the general transcription machinery. However, there was no evidence that **CIITA** actually functions at the level of MHC-II promoters. Physical interactions between **CIITA** and MHC-II promoter binding proteins have not been reported. In conclusion, the data presented here demonstrate that **CIITA** is a transcriptional co-activator that is recruited to the MHC-II enhanceosome via multiple protein-protein interactions with DNA bound activators. Factors binding to the W, X, X2 and Y sequences are all involved in creating the **CIITA** docking interface. This is in full agreement with previously published data demonstrating that **CIITA** exerts its function via these four promoter sequences. The mechanism documented here is characteristic for recruitment of components of the general transcription machinery. **CIITA** however, is a gene specific regulatory co-activator that is not part of the general transcription machinery. The approach we have developed here can now be exploited to address several unresolved issues concerning the mode of action of **CIITA**, including which additional known or unknown factors it brings to the MHC-II promoter, which general transcription factors it is capable. . . . by DNA bound factors. The MHC-II enhanceosome consists of ubiquitously expressed DNA-binding proteins that serve as a landing pad for **CIITA**. In contrast, **CIITA** is expressed in a highly regulated pattern that governs the cell type specificity, induction and level of MHC-II expression. Moreover, genetic evidence derived from MHC-II deficiency patients and knockout mice has demonstrated that **CIITA** is highly specific for MHC-II genes. **CIITA** is thus a paradigm for a novel type of co-activator that acts both as a specificity factor and as a. . . unique, or have co-activators with similar properties not yet been identified in other systems? Via its control over MHC-II expression **CIITA** plays a key role in the regulation of adaptive immune responses.

SUMM . . . motif), to allow the interaction between the RFX complex and at least one of the transcription factors X2BP, NF-Y or **CIITA**, to allow a cooperative interaction that stabilizes the higher order RFX-X2BP-NF-Y complex, to direct contacts between RFX and the co-activator **CIITA**, to allow binding of RFX5 to the X box, or to correct the MHC II expression defect of cell lines. . .

SUMM . . . having the amino acid sequence shown in FIG. 2 (RFX-ANK) is to allow the interaction between the RFX complex and **CIITA**, to allow a cooperative interaction that stabilizes the higher order RFX-X2BP-NF-Y complex, to direct contacts between RFX and the co-activator **CIITA** or the recruitment of **CIITA**.

SUMM . . . relates to a protein complex comprising cellular proteins capable of binding to the W-X-X2-Y box of MHC-class II promoters and **CIITA**.

SUMM [0053] A protein complex as mentioned above may comprise a **CIITA** wich is chosen in the following group: a recombinant or recombinantly produced **CIITA**, a mutant **CIITA**, a mutant **CIITA** which has greater affinity for the MHC-class II enhanceosome than a wild-type **CIITA** and a truncated version of a wild-type **CIITA**.

SUMM [0072] In a further embodiment, the invention relates to an anti-sense molecule or a **ribozyme** comprising a nucleic acid molecule or a polynucleotide as recited in the preceding paragraph.

SUMM . . . a vector comprising a nucleic acid molecule of the invention or being able to express an anti-sense molecule or a **ribozyme** of the invention.

SUMM . . . the invention may be the capacity to enable the functional transcription of MHC class II genes, via the recruitment of **CIITA**, and consequently the expression of MHC class II gene products.

SUMM [0081] The recruitment of **CIITA** may be defined as the binding or fixation of **CIITA** to the MHC-class II enhanceosome. The

MHC-class II enhanceosome may be defined as the complex between a fragment of DNA. . .

SUMM . . . motif, to allow the interaction between the RFX complex and at least one of the transcription factors X2BP, NF-Y or **CIITA**, to allow a cooperative interaction that stabilizes the higher order RFX-X2BP-NF-Y complex, to direct contacts between RFX and the co-activator **CIITA**, to allow binding of RFX5 to the X box, or to correct the MHC II expression defect of cell lines. . .

SUMM . . . of interest of the invention (transcription factor of the invention) is to allow the interaction between the RFX complex and **CIITA**, to allow a cooperative interaction that stabilizes the higher order RFX-X2BP-NF-Y-complex, to direct contacts between RFX and the co-activator **CIITA** or the recruitment of **CIITA**.

SUMM . . . specific action limited to MHC class II genes because their target, ie transcription factor of the invention or recruitment of **CIITA** has specificity restricted to promoters of MHC class II genes.

SUMM [0093] Recruitment of **CIITA** is essential for MHC-class II transcription because this recruitment governs all spatial, temporal and quantitative aspects of MHC-class II expression. Furthermore, **CIITA** is a MHC-class II-specific co-activator.

SUMM . . . to the X box motif, to allow the interaction between the RFX complex and the transcription factor X2BP, NF-Y or **CIITA** to allow a cooperative interaction that stabilizes the higher order RFX-X2BP-NF-Y complex, to direct contacts between RFX and the co-activator **CIITA**, to allow binding of RFX5 to the X box, or to correct the MHC II expression defect of cell lines. . .

SUMM . . . embodiment, a function or activity of the invention is to allow the interaction between the RFX complex and the transcription **CIITA**, to allow a cooperative interaction that stabilizes the higher order RFX-X2BP-NF-Y complex, to direct contacts between RFX and the co-activator **CIITA** or recruitment of **CIITA**.

SUMM . . . the detected function is interaction between the RFX complex and at least one of the transcription factor X2BP, NF-Y and **CIITA**.

SUMM . . . the capacity to inhibit interaction between the RFX complex and at least one of the transcription factors X2BP, NF-Y and **CIITA**

.

SUMM . . . mixing of the candidate inhibitor with the RFX complex and at least one of the transcription factors X2BP, NF-Y and **CIITA**.

SUMM [0132] In a fifth embodiment, the detected function is interaction between the RFX complex and **CIITA**.

SUMM . . . relates to a process for identifying an inhibitor which has the capacity to inhibit interaction between the RFX complex and **CIITA**.

SUMM . . . process may comprise the mixing of the candidate inhibitor with the RFX complex and the transcription factors X2BP, NF-Y and **CIITA**.

SUMM [0138] The stabilization of the higher order RFX-X2BP-NF-Y complex may be done by **CIITA**.

SUMM [0139] Said process may comprise the mixing of the candidate inhibitor with the transcription factors RFX, X2BP, NF-Y and **CIITA**.

SUMM [0141] In a seventh embodiment, the detected function is recruitment of **CIITA** or the binding or fixation of **CIITA** to the MHC-class II enhanceosome.

SUMM [0142] The invention relates to a process for identifying an inhibitor which has the capacity to inhibit recruitment of **CIITA** or to inhibit the binding or fixation of **CIITA** to the MHC-class II enhanceosome. The MHC-class II enhanceosome may be defined as the complex between a fragment of DNA. . .

SUMM [0143] In an eighth embodiment, the invention relates to a process for identifying dominant negative mutants of **CIITA** inhibitor which have the capacity to inhibit recruitment of **CIITA** or to inhibit the binding or fixation of wild-type **CIITA** to the MHC-class II enhanceosome.

SUMM [0147] If the substance does not inhibit the interaction between the RFX complex and **CIITA**, then **CIITA** binds to the RFX complex which binds to the DNA and the DNA-protein association migrates slower than the non-DNA bound **CIITA**-RFX complex.

SUMM [0148] If the substance does not inhibit the stabilization of the RFX-X2BP-NF-Y complex by **CIITA** RFX-X2BP-NF-Y, then **CIITA** binds to the RFX-X2BP-NF-Y complex which binds to the DNA and the DNA-protein association migrates slower than the non-DNA bound **CIITA**-RFX complex.

SUMM [0149] If the substance does not inhibit the recruitment of **CIITA**, then **CIITA** binds to the MHC-class II enhanceosome which migrates slower than the non-DNA bound proteins.

SUMM . . . MHC II promoters is contacted with a mixture of cellular proteins comprising proteins binding to the W-X-X2-Y box region and **CIITA**, and with the substance to be tested;

SUMM [0154] iii) the presence or absence of **CIITA** in the proteins obtained after step iii) is detected, absence of **CIITA** indicating that the substance under test has a capacity to inhibit **CIITA** recruitment.

SUMM [0155] The invention relates to a process for identifying an inhibitor which has the capacity to inhibit recruitment of **CIITA** or to inhibit the binding or fixation of **CIITA** to the MHC-class II enhanceosome which comprises the following steps:

SUMM [0159] iv) the presence of **CIITA** in the proteins obtained after step iii) is detected.

SUMM [0160] A process for identifying an inhibitor which has the capacity to inhibit recruitment of **CIITA** or to inhibit the binding or fixation of **CIITA** to the MHC-class II enhanceosome recited above may be used in a primary screening or in a secondary (confirmatory screening).

SUMM [0167] In the above process, the presence of **CIITA** in the proteins obtained after step iii) is preferably detected by antibodies specific of **CIITA**.

SUMM [0168] In the above process, **CIITA** is preferably chosen among: a recombinant or recombinantly produced, a mutant **CIITA**, a mutant **CIITA** which has greater affinity for the MHC-class II enhanceosome than a wild-type **CIITA**, a truncated version of a wild-type **CIITA**.

SUMM [0169] In the above process, **CIITA** is preferably tagged, especially with a Fluorescent Protein or an epitope.

SUMM [0170] In the above process, the substances to be tested may be **CIITA** dominant negative mutants.

SUMM [0171] In the above process, the mixture of cellular proteins and **CIITA** preferably comprises a nuclear extract of **CIITA**+ cells

SUMM [0174] In the above-mentioned process, the presence of **CIITA** in the proteins obtained after step iii) is advantageously detected by antibodies. These antibodies are preferably specific of **CIITA** but may be specific of RFX or NF-Y. Preferably, the presence of **CIITA** in the proteins obtained after step iii) is detected by Western-Blot.

SUMM . . . II- cell. If a nuclear extract of a cell comes from an MHC-class II- cell, a recombinant or recombinantly produced **CIITA** is added to the nuclear extract. This recombinant or recombinantly produced **CIITA** may be a mutant CITA. A mutant **CIITA** may be chosen in order to have greater affinity for the MHC-class II enhanceosome than a wild-type **CIITA**. A recombinant or recombinantly produced **CIITA** may preferably be detected directly. Thus, a recombinant or recombinantly produced **CIITA** may be fused to a molecule which can be directly detected. A molecule which can be directly detected may be a Green Fluorescent Protein. A recombinant or recombinantly produced **CIITA** may be fused to an epitope which can be directly detected by antibodies specific to this epitope.

SUMM [0189] Said inhibitors may be a **ribozyme**, a DNA or a RNA

antisense.

SUMM [0190] Said inhibitors may be a **ribozyme**, a DNA or a RNA **antisense** of the invention as recited above.

SUMM [0191] Complementary nucleotide sequence of the nucleic acid molecule of the invention, also referred to as <<**antisense**>> RNA or DNA are known to be capable of inhibiting the synthesis of the protein encoded by the revelant nucleic. . .

SUMM . . . nucleic acid molecule sequences of the invention mentioned above will be in a position to produce and utilize the corresponding << **antisense**>> RNA and DNA and to use them for the inhibition of synthesis of the transcription factor of the invention.

SUMM [0194] The use of <<**antisense**>> RNA and DNA molecules, as described above, as inhibitors of MHC class II gene expression will be important in medical. . .

SUMM . . . also relates to fragments of said nucleotide sequences, preferably to fragments of their coding regions, including fragments of complementary or <<**antisense**>> RNA and DNA. The person skilled in the art and provided with the sequences described above is in a position to produce the corresponding short <<**antisense**>> aligonucleotides and to use them to achieve inhibition of a transcription factor of the invention synthesis and therefore inhibition of. . .

SUMM [0223] The knowledge of the recruitment of **CIITA** recited in this application allows to define the protein-protein contacts that contribute to **CIITA** recruitment and therefore to lead to the development of novel inhibitors that function by interfering with these protein-protein interactions.

SUMM . . . comprising a DNA fragment comprising the W-X-X2-Y region of the MHC-class II promoters and means to detect the presence of **CIITA** in a sample. Means to detect the presence of **CIITA** in a sample may be a recombinant **CIITA** comprising a tagging molecule. A tagging molecule may be an epitope or a fluorescent protein.

SUMM . . . respective complementation groups, the number of patients reported, and the chromosomal location of each of the corresponding gene are indicated. **CIITA** is a highly regulated non-DNA binding co-activator that is responsible for cell-type specificity and inducibility of MHC-II expression. RFX5, RFXAP. . .

SUMM [0282] FIG. 9: Binding of **CIITA** to the MHC-II Enhanceosome.

SUMM . . . complexes assembled on the promoter fragment (+) or in the presence of non-specific DNA (-) were immunoprecipitated with antibodies against **CIITA**, the RFXAP subunit of RFX, or pre-immune serum (P.I.). Immunoprecipitates were analyzed by immunoblotting with antibodies against **CIITA**, the RFX5 subunit of RFX, and the B subunit of NF-Y.

SUMM [0284] FIG. 10 Recruitment of **CIITA** Requires Multiple Promoter Binding Factors.

SUMM . . . W, X, X2 or Y boxes, and a deletion of the octamer site (.DELTA..smallcircle.), were tested for their effect on **CIITA** recruitment in a promoter pull-down assay. Mutated or wild type (wt) promoter fragments immobilized on magnetic beads were incubated with a RJ6.4 extract. Proteins purified by the pull down assay were analyzed by immunoblotting for the presence of **CIITA**, RFX5, NF-YB and OBF-1. 3% of the input extract (-) was analyzed in parallel to visualize the enrichment obtained.

SUMM [0288] FIG. 11: Mutations of **CIITA** Affecting Recruitment.

SUMM [0289] (a) Schematic representation of wild type (wt) and mutant **CIITA** proteins. The acidic and proline/serine/threonine rich activation domains, GTP-binding cassette and leucine-rich repeat (LRR) region are indicated.

SUMM [0291] (c, d) Pull-down assays were performed with RJ2.2.5 extracts supplemented with the indicated recombinant **CIITA** proteins. 1% of the input extract (-) and proteins purified by the pull down assay (+) were analyzed by immunoblotting. The C-terminal **CIITA** antibody was used in part c.

DETD . . . was also transfected into cell lines from complementation

groups A (RJ2.2.5), C (SJO) and D (Da), which carry mutations in **CIITA**, RFX5 and RFXAP, respectively.sup.8-10, 15.

DETD [0334] Recruitment of **CIITA** Assay

DETD . . . 1993 ID: 1242} and Villard et al, submitted). The RJ6.4 cell line was produced by stable transfection of RJ2.2.5 with **CIITA** tagged at its N-terminus with a haemagglutinin epitope (V. Steimle, unpublished). Cell culture, transfections, selection with hygromycin, and flow cytometry. . .

DETD [0337] Extracts and Recombinant **CIITA** Expression.

DETD . . . Roche Diagnostics). Whole cell extracts were obtained by 3 freeze-thaw cycles, cleared by centrifugation and stored at -80.degree. C. Recombinant **CIITA** proteins were expressed in HeLa cells using a Vaccinia-T7 system, and extracts from these cells were prepared as above.

DETD [0341] DNA-dependent Immunoprecipitation and Promoter Pull-down Assays (Recruitment of **CIITA** Assay).

DETD . . . A-Sepharose beads (Pharmacia) for 30 minutes and cleared by centrifugation. Supernatants were then incubated for 1 hour with anti-RFXAP or anti-**CIITA**-N antibodies coupled to protein-A-Sepharose. The beads were washed thrice with buffer D (20 mM HEPES pH 7.9, 100 mM KCl,. . . cell extracts was, respectively, 100% and 20-50%. Due to low affinity for the enhanceosome, typically less than 1% of the **CIITA** was recruited. The **CIITA** concentration was found to be the limiting factor for the interaction. This is consistent with previous findings indicating that the concentration of **CIITA** is the limiting factor in MHC-II transcription. The low affinity of the interaction ensures that recruitment of CITA to MHC-II. . . range. Experiments in FIGS. 9 and 10 were performed with extracts from RJ6.4 cells expressing 2 to 3 times more **CIITA** than the B cell line Raji. This led to a proportional increase in **CIITA** recruitment, thereby yielding neater results having a higher signal-to-noise ratio. Notwithstanding, identical results were obtained with Raji cells. Extending the promoter template upstream to position -196 or downstream to +51 did not improve enhanceosome assembly or recruitment of **CIITA**. In experiments with recombinant **CIITA**, extracts from RJ2.2.5 and HeLa cells expressing the recombinant proteins were mixed before adding the other reaction components. Concentrations of recombinant **CIITA** added to the assembly reactions were comparable to the endogenous **CIITA** concentration in B cell extracts.

DETD [0344] Antibodies specific for the N-terminus of **CIITA** (anti-**CIITA**-N, used in FIGS. 9, 10, 11d) were obtained by affinity purification of a polyclonal anti-**CIITA** serum on a N-terminal His.sub.6-tagged **CIITA** fragment (aa 25-300) covalently coupled to Sepahrose beads. Antibodies specific for the C-terminus of **CIITA** (anti-**CIITA**-C, used in FIG. 11c) were retrieved from the unbound fraction by a second affinity purification step using full-length recombinant **CIITA**. RFX5 antibodies and immunoaffinity-purified RFXAP antibodies have been described. The NF-YB antibody was a gift from Roberto Mantovani. The TBP. . . Proteins were analyzed by immunoblotting according to standard protocols. In immunoblots done with B cell extracts (FIGS. 9 and 10), **CIITA** is detected as a double band, probably due to the use of alternative initiation codons.

DETD [0346] We hypothesized that recruitment of **CIITA** to MHC-II promoters might require the synergistic contribution of weak interactions with multiple enhanceosome components. To test this, we performed immunoprecipitations with B cell extracts and antibodies directed against **CIITA** or RFX, in the presence of a prototypical MHC-II promoter (DRA) fragment permitting enhanceosome assembly (FIG. 8). The immunoprecipitates were analyzed for the presence of **CIITA**, RFX and NF-Y (FIG. 9). Co-immunoprecipitation of the three factors was observed only when the promoter fragment was included, demonstrating formally that **CIITA** interacts physically with the assembled enhanceosome but not with isolated components such as RFX

or NF-Y. The trace amount of **CIITA** that co-immunoprecipitates with RFX in the absence of promoter DNA does not reflect a specific RFX-**CIITA** interaction because it is also observed when pre-immune serum is used. In contrast, the small amount of NF-Y that co-purifies.

. .

DETD [0347] To identify enhanceosome components critical for **CIITA** recruitment we developed a pull-down assay employing wild type and mutated DRA promoter templates immobilized on magnetic beads. Recruitment of **CIITA** to the enhanceosome is demonstrated by co-purification of **CIITA** with RFX and NF-Y when B cell extracts and the wild type template is used (FIG. 10a). The same is observed using extracts from MHC-II negative cells (HeLa, HEK 293) tansfected with **CIITA** (data not shown), indicating that the enhanceosome components required for recruitment are not B cells specific. This is consistent with the fact that transfection with **CIITA** is sufficient activate MHC-II expression in such MHC-II negative cells. The pull down assay is specific because no purification is. . . (TBP, TAF250) or the co-activator CBP (data not shown). Mutations of the W, X2 and Y boxes all strongly reduced **CIITA** recruitment (FIG. 10a). The Y mutation specifically eliminates binding of NF-Y, indicating that this protein is crucial for **CIITA** recruitment. The drastic effect of the W and X2 mutations also demonstrates the importance of X2BP and W binding factors for CITA recruitment. These factors are likely to provide direct contacts with **CIITA** because the X2 and W mutations do not interfere with binding of RFX or NF-Y. Unfortunately, purification of the relevant. . CREB-1 was not enriched consistently by the pull down assay and we could not show that it is required for **CIITA** recruitment (data not shown).

DETD . . . octamer site abolished retention of OBF-1 in the pull down assay, but this had no detectable effect on binding of **CIITA** (FIG. 10a). We conclude that the octamer site and its cognate activator proteins are not required for tethering of **CIITA** to the promoter. This is not surprising considering that the DRA promoter is the only MHC-II promoter that contains an octamer site. Surprisingly, the X mutation had no effect on **CIITA** recruitment (FIG. 10a). However, it also did not eliminate binding of RFX (FIG. 10a). This was unexpected because the X. . .

DETD [0349] To determine whether the RFX complex is required for **CIITA** recruitment we used cell lines derived from MHC-II deficiency patients having mutations in the genes encoding its three subunits (RFX5, RFXAP and RFXANK). Binding of RFX and recruitment of **CIITA** are not observed in pull-down assays performed with extracts from the RFX5-deficient cell line SjO (FIG. 10b). Identical results were obtained with cell lines lacking RFXAP or RFXANK (data not shown). Binding of RFX, recruitment of **CIITA** and MHC-II expression are restored in SJO cells complemented with RFX5 (FIG. 10b, c). This confirms that incorporation of RFX into the enhanceosome is essential for recruitment of **CIITA** and promoter activation.

DETD [0350] To define domains within **CIITA** that are implicated in recruitment, we used a **CIITA** deficient extract (RJ2.2.5) that was supplemented with recombinant wild type or mutant **CIITA**. Two dominant negative mutants (.DELTA.5 and L335) lacking the N-terminal transcription activation domains were tested (FIG. 11a). Transfection of MHC-II. . . expression (FIG. 11b). .DELTA.5 and L335 retain their ability to bind to the enhanceosome, indicating that the C-terminal moiety of **CIITA** is sufficient (FIG. 11c). Remarkably, recruitment of .DELTA.5 and L335 was considerably more efficient than that of wild-type **CIITA**, indicating that their dominant negative phenotype can be explained by an increased affinity for the enhanceosome. This would lead to competitive inhibition of wild type **CIITA** recruitment in transfected cells, which typically express the mutant proteins at levels greater than that of the endogenous protein. Two. . . interaction domain consisting of leucine rich repeats (LRR). The BCH and BLS-2 mutants were recruited less efficiently

than wild type **CIITA** (FIG. 11d) Deletion of sequences involved in recruitment is thus likely to account, at least in part, for their loss of function phenotype. The finding that the BLS-2 and BCH mutations inhibit recruitment only partially suggests that **CIITA** contains more than one region involved in binding to the enhanceosome. This is in agreement with the fact that multiple DNA binding proteins form the landing pad for **CIITA** (FIG. 10).

DETD [0351] Multiple **CIITA**-enhanceosome interactions would be expected to exert a reciprocal stabilization effect. They would not only enhance binding of **CIITA**, but also contribute to promoter occupancy by stabilizing interactions between the components of the enhanceosome. Stabilization of the enhanceosome by **CIITA** could underlie a number of unexplained observations. First, in certain cell types, in vivo occupation of MHC-II promoters requires expression of **CIITA**. Second, in certain RFX-deficient cells, over expression of **CIITA** can lead to a partial rescue of MHC-II expression. Finally, RFX5 -/- mice exhibit residual MHC-II expression in cell types that are likely to express high levels of **CIITA**.

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DETD [0411] 59. Mahanta, S. K., Scholl, T., Yang, F. C. & Strominger, J. L. Transactivation by **CIITA**, the **type II bare lymphocyte syndrome-associated factor**, requires participation of multiple regions of the TATA box binding protein. Proc. Natl. Acad. Sci. U. S. A. 94, 6324-6329.

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DETD [0413] 61. Zhou, E. & Glimcher, L. H. Human MHC class II gene transcription directed by the carboxyl terminus of **CIITA**, one of the defective genes in type II MHC combined immune deficiency. Immunity 2, 545-553 (1995).

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DETD [0425] 73. Wright, K. L. et al. **CIITA** stimulation of transcription factor binding to major histocompatibility complex class II and associated promoters in vivo. Proc. Natl. Acad. Sci.. . .

DETD [0428] 76. Chang, C. H., Guerder, S., Hong, S. C., van Ewijk, W. & Flavell, R. A. Mice lacking the **MHC class II**

transactivator (**CIITA**) show tissue-specific impairment of MHC class II expression. IMMUNITY. 4, 167-178 (1996).

CLM What is claimed is:

19. Anti-sense molecule or **ribozyme** comprising a nucleic acid molecule of claim 13 or 18.

. . . function or activity is the interaction between the RFX complex and at least one of transcription factors X2BP, NF-Y and **CIITA**.

39. Process for identifying an inhibitor which has the capacity to inhibit recruitment of **CIITA** or to inhibit the binding or fixation of **CIITA** to the MHC-class II enhanceosome, said process comprising the following steps: i) a DNA fragment consisting or comprising the W-X-X2-Y. . . MHC II promoters is contacted with a mixture of cellular proteins comprising proteins binding to the W-X-X2-Y box region and **CIITA**, and with the substance to be tested ; ii) the thus formed DNA-protein complex is separated from the reaction mixture; iii) the presence or absence of **CIITA** in the proteins obtained after step ii) is detected, absence of **CIITA** indicating that the substance under test has a capacity to inhibit **CIITA** recruitment.

44. Process according to any one of claim 39 to 43, wherein the presence of **CIITA** in the proteins obtained after step iii) is detected by antibodies specific of **CIITA**.

45. Process according to any one of claim 39 to 44, wherein **CIITA** is chosen among: a recombinant or recombinantly produced, a mutant **CIITA**, a mutant **CIITA** which has greater affinity for the MHC-class II enhanceosome than a wild-type **CIITA**, a truncated version of a wild-type **CIITA**.

46. Process according to any one of claims 39 to 45, wherein **CIITA** is tagged or wherein **CIITA** comprises a Fluorescent Protein or an epitope.

47. Process according to any one of claims 39 to 46, wherein the substances to be tested are **CIITA** dominant negative mutants.

48. Process according to any one of claims 39 to 47, wherein the mixture of cellular proteins and **CIITA** comprises a nuclear extract of **CIITA**+ cells.

. . . of a nucleic acid molecule according to any one of claims 11 to 18, or an anti-sense molecule or a **ribozyme** according to claim 19.

. . . an antibody, a single chain antibody, a dominant negative mutant, a protein, a peptide, a small molecular weight molecule, a **ribozyme** or an anti-sense molecule.

59. Protein complex comprising cellular proteins capable of binding to the W-X-X2-Y box of MHC-class II promoters and **CIITA**.

60. Protein complex according to claim 59 wherein **CIITA** is: a recombinant or recombinantly produced **CIITA**, a mutant **CIITA**, a mutant **CIITA** which has greater affinity for the MHC-class II enhanceosome than a wild-type **CIITA** or a truncated version of a wild-type **CIITA**.

L3 ANSWER 15 OF 47 USPATFULL
ACCESSION NUMBER: 2002:273560 USPATFULL
TITLE: NUCLEIC ACID SEQUENCES OF **CIITA** GENES WHICH CAN BE INVOLVED IN CONTROLLING AND REGULATING THE EXPRESSION OF GENES ENCODING MHC TYPE II MOLECULES, AND THEIR USE, IN PARTICULAR AS DRUGS.

INVENTOR(S): MACH, BERNARD, GENEVA, SWITZERLAND

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PRIORITY INFORMATION:	FR 1997-4954	19970422

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LEGAL REPRESENTATIVE: BURNS DOANE SWECKER & MATHIS L L P, POST OFFICE BOX 1404, ALEXANDRIA, VA, 22313-1404

NUMBER OF CLAIMS: 59
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI NUCLEIC ACID SEQUENCES OF **CIITA** GENES WHICH CAN BE INVOLVED IN CONTROLLING AND REGULATING THE EXPRESSION OF GENES ENCODING MHC TYPE II MOLECULES, AND THEIR. . .

AB The present invention relates to nucleic acid sequences which comprise all or part of a nucleic acid sequence of a **CIITA** gene. These sequences can comprise a sequence which exhibits a transcriptional promoter activity, which activity is, in particular, specifically expressed. . .

SUMM [0009] The applicant has previously identified and characterized one of these factors, i.e. the **CIITA** factor (class II transactivator) [Steimle et al., 1993, Cell 75, 135-146 and EP 648836]. Furthermore, document WO 9606107 shows that there are two domains within the **CIITA** factor which are more involved in activating transcription of the MHC class II genes, more specifically the domain which is. . . II genes (Cogswell et al., 1991, Crit. Rev. Immunol. 11, 87-112), Steimle et al. have demonstrated that expression of the **CIITA** factor coincides strictly with expression of the MHC class II genes and is required absolutely both for constitutively expressing and. . . suppression of the MHC class II genes during plasma cell differentiation is associated with suppression of the gene which encodes **CIITA** factor.

SUMM [0010] Moreover, Lennon et al. (1997, Immunogenetics, 45, 266-273) have identified the promoter sequence of a **CIITA** gene, which sequence is responsible for the differential expression of this factor in B cells. However, the existence of this sequence alone does not explain why differential expression of the **CIITA** factor is observed in different cell types. Furthermore, it does not account for induction by cytokines.

SUMM . . . origin, the applicant has now identified the complex organization of the sequences which ensure regulation of the expression of the **CIITA** factor, has isolated and characterized other promoter regions and has demonstrated the existence of several forms of **CIITA** factor, and has also demonstrated the existence of different **CIITA** genes.

SUMM [0012] The expression "**CIITA** gene" is understood as meaning a nucleic acid sequence which consists of a promoter (P) moiety, an untranslated (UT) moiety and a coding (Prot) moiety, with the coding moiety encoding one of the identified forms of **CIITA** factor.

SUMM [0013] More precisely, the inventors have identified a number of nucleic acid sequences which represent **CIITA** genes and which are therefore capable, in particular, of being involved in controlling and regulating the expression of genes encoding MHC class II molecules. The expression "nucleic acid sequence which represents **CIITA** genes" is understood as meaning that the sequence in question comprises all or part of a nucleic acid sequence corresponding to the mRNAs which derive from the different tissues or cell lines which express

CIITA activity either constitutively or following induction. Such sequences can therefore equally well be sequences which are at least partially coding,. . .

SUMM . . . a functional link with the said first sequence. Thus, according to the invention, a nucleic acid sequence which exhibits a **CIITA** promoter activity, that is which naturally directs the transcription of a nucleic acid sequence encoding a **CIITA** factor, is, for example, considered as being homologous to this same nucleic acid sequence which encodes a **CIITA** gene. In the opposite case, reference will be made to a "heterologous nucleic acid sequence".

SUMM . . . invention thus relates to a nucleic acid sequence which comprises all or part of a nucleic acid sequence of a **CIITA** gene and which is selected from the sequences SEQ ID No. 1, SEQ ID No. 2 and SEQ ID No.. . .

SUMM . . . or their fragments, can, in particular, encode all or part of polypeptides which possess the amino acid sequence of a **CIITA** factor as described in the present invention.

SUMM [0037] It will then be stated that they encode **CIITA** polypeptides.

SUMM . . . target sequence which belongs to a gene or to an RNA whose expression it is desired to block specifically. An **antisense** oligonucleotide which hybridizes with the sequence to which it is complementary and can thereby block expression of the mRNA having. . .

SUMM . . . is located downstream of the said sequence, or to a change in the coding sequence which affects expression of the **CIITA** gene, or to a change in the encoded amino acid as compared with the normal sequence, which change affects the function of the corresponding **CIITA** factor.

SUMM . . . said gene of interest can, for example, be selected from the group which consists of the genes which encode the **CIITA** factor and the .alpha. and .beta. chains of the HLA-DR, HLA-DQ and/or HLA-DP molecules, and reporter genes, such as the. . .

SUMM . . . such as previously described, in particular in order to ensure expression of at least one of the forms of the **CIITA** factor which have been identified in accordance with the invention.

SUMM [0056] The cells which have thus been obtained can be used to prepare natural or mutated **CIITA** polypeptides and also fragments of these polypeptides.

SUMM . . . type. These cells can additionally be used as model cells for the purpose of studying the interactions between the different **CIITA** factors which have been isolated, or their variants, and the regions which direct transcription of the genes encoding the MHC class II molecules, and, especially, for the purpose of selecting the variants of the **CIITA** factors which are able to act as agonists or antagonists on the **CIITA** receptor. These types of cell model can be constructed using known techniques of genetic manipulation. Furthermore, the use of such. . .

SUMM [0059] The present invention also relates to a process for producing a **CIITA** polypeptide, in particular as defined in SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18 or SEQ. . . (i) culturing a host cell, which has been transformed with a vector which includes a nucleic acid sequence encoding a **CIITA** polypeptide as previously described, under culture conditions which are appropriate for producing the said polypeptide, and (ii) recovering the said. . .

SUMM [0061] The present invention also relates to a **CIITA** polypeptide which can be obtained by implementing the abovedescribed process.

SUMM [0062] The present invention additionally relates to **CIITA** polypeptides which correspond to the previously described nucleic acid sequences and which are in unnatural form, i.e. they are not. . .

SUMM . . . retro and/or inverso and which exhibit an activity which is equivalent to that observed in the case of the native **CIITA** factor, or one of its variants, according to the present invention, or at least an immunological activity which is identical to that of the parent **CIITA** factor.

SUMM . . . described, can exhibit the same function of transactivating the expression of the genes encoding MHC class II molecules as a **CIITA** factor or, at least, the same ability to bind to the specific site for binding a **CIITA** factor during expression of the said genes.

SUMM . . . of the previously described polypeptides or against a polypeptide which contains at least one mutation affecting the function of the **CIITA** factor, as described below, and, more specifically, to a polyclonal or monoclonal antibody which is obtained by the immunological reaction. . .

SUMM . . . expression of the genes encoding the MHC class II molecules or the ability of these polypeptides to bind to the **CIITA**-binding site. These molecules can be polypeptides which contain at least one mutation which affects the function of the **CIITA** factor. A modified polypeptide of this nature, which consists, for example, of a structural analogue of the said polypeptide, can. . . also be antibodies, such as presented above, which are able, for example, to block either all or part of the **CIITA** factor which is able to react with its specific receptor, or a region of the **CIITA** factor which is able to interact with at least one other transactivating factor during expression of the genes encoding the. . .

SUMM . . . such that the promoter activity of the said sequence is affected, or which leads to the production of an inactive **CIITA** polypeptide, as previously described, or b) an inactive **CIITA** polypeptide.

SUMM . . . least one mutation, within either sequences which exhibit a transcriptional promoter activity or sequences which encode one of the identified **CIITA** factors according to the present invention, is determined by analysing the said nucleic acid sequences and comparing with the wild-type. . .

SUMM [0082] Furthermore, the mutated **CIITA** factors which are found in subjects who are exhibiting disorders in the expression of the genes encoding MHC type II molecules can exhibit an antigenicity which is different from that of the identified natural **CIITA** factors SEQ ID No. 16, SEQ ID No. 17 or SEQ ID No. 18. It is therefore possible to diagnose. . . the expression of the genes encoding MHC type II molecules by demonstrating the presence of the product of the mutated **CIITA** gene, for example using antibodies, in particular monoclonal antibodies, as previously described.

DRWD [0085] FIG. 1 depicts the four 5' ends of the **CIITA** mRNAs which were identified as described in Example 1. The coding regions are indicated by the wide boxes while the. . .

DRWD . . . sites for binding known transcription factors which were identified on the sequence, of the 5'-flanking region of the type I **CIITA** gene. The main transcription initiation site is also indicated by an arrow at +1.

DRWD . . . sites for binding known transcription factors which were identified on the sequence, of the 5'-flanking region of the type III **CIITA** gene. The main transcription initiation site is also indicated by an arrow at +1.

DRWD . . . sites for binding known transcription factors which were identified on the sequence, of the 5'-flanking region of the type IV **CIITA** gene. The main transcription initiation site is also indicated by an arrow at +1.

DRWD . . . the probes which were used in the RNAse protection tests during the analysis of the expression profiles of the different **CIITA** mRNAs. The different probes are shown with their sizes "before" and "after" digestion by RNAse. Each of the probes corresponds. . .

DRWD [0090] FIG. 6 is a diagrammatic representation of the differential expression of the four types of **CIITA** transcript. The quantity of each of the mRNA types is indicated as a percentage as compared with the total quantity of **CIITA** expression, as measured using the internal control and after PhosphoImager quantification of the fragments which were obtained following the RNAse. . .

DRWD . . . FIG. 7 is a diagrammatic representation of the same type as

that in FIG. 6 except that expression of the **CIITA** transcripts is observed following induction with interferon .alpha.(+IFN.gamma.).

DETD . . . SEQ ID No. 1 to SEQ ID No. 3: the sequences of the three types of cDNA corresponding to the **CIITA** genes (sequences designated I, II and IV in FIG. 1), which were identified in accordance with the invention;

DETD . . . the sequences which were identified as exhibiting a transcriptional promoter activity in the form I, form II and form IV **CIITA** genes and which were designated PI, PII and PIV, respectively;

DETD [0097] SEQ ID No. 7 to SEQ ID No. 10: the sequences which correspond, respectively, to the different **CIITA** genes of forms I to IV, which genes lack the sequences which exhibit a transcriptional promoter activity;

DETD [0098] SEQ ID No. 11: the sequence which corresponds to the coding part of the form I **CIITA** gene;

DETD [0099] SEQ ID No. 12: the sequence which corresponds to the coding part of the form II **CIITA** gene;

DETD [0100] SEQ ID No. 13: the sequence corresponding to the coding part of the form III **CIITA** gene;

DETD [0101] SEQ ID No. 14: the sequence corresponding to the coding part of the form IV **CIITA** gene, including a untranslated part;

DETD [0103] SEQ ID No. 16: the translation of SEQ ID No. 11 into amino acids, corresponding to a form I **CIITA** factor which possesses 101 additional amino acids at the N-terminal end, as compared with SEQ ID No. 17;

DETD . . . SEQ ID No. 17: the translation into amino acids of the coding part of the form I to form IV **CIITA** genes, starting from an ATG located 21 bases downstream of the 5' end of the common exon 2 (FIG. 1);

DETD [0105] SEQ ID No. 18: the translation of the form III **CIITA** gene into amino acids, starting from a second ATG, and corresponding to a **CIITA** factor which possesses 24 additional amino acids at the N-terminal end;

DETD . . . 200 .mu.M of each of the dNTPs and 25 pmol of primers which are specific for the gene encoding the **CIITA** factor, i.e. P1 (5'-GTCCAGTTCCGCGATATTGG-3') and P2 (5'-TCCCTGGTCTCTTCATCA-3'), 25 pmol of adaptation primer ADXSC (5'-GACTCGAGTCGACATCG-3') and 10 pmol of adaptation primer. . .

DETD [0110] These amplifications demonstrated the existence of four types of cDNA which corresponded to the **CIITA** factor. Analysis of the sequences of these nucleic acids showed that while these nucleic acids all possessed a common 3'. . .

DETD . . . initiation codon. In the case of sequences I and III, another ATG exists which leads to the synthesis of a **CIITA** factor which possesses 101 or 24 additional amino acids, respectively, at the N-terminal end of the translated polypeptide.

DETD [0112] The sites for initiating transcription of the different human **CIITA** mRNAs which had been identified were tested by means of RNAse protection using DNA fragments which were specific for the. . .

DETD . . . FIG. 5. Use is made of an internal control which makes it possible to evaluate the total expression of the **CIITA** -encoding genes (from nucleotide 1152, PstI site, to nucleotide 1344, NcoI site, protecting 193 bases of the region possessed in common. . . being the ratio of the expression of a specific type of mRNA as compared with the total expression of the **CIITA**-encoding genes measured using the internal control.

DETD . . . analysis was carried out of the mRNAs which were derived from different tissues or cell lines which were expressing the **CIITA** gene either constitutively or following induction with interferon .gamma..

DETD . . . respectively, before induction and of 7.9 and 29.6, respectively, following induction with interferon.

TABLE 1

Percentages of the different types of **CIITA** mRNA observed in various tissues and cell lines.

	TYPE I	TYPE III	TYPE IV
Spleen	3.5%	67%	33%
Tonsil	0%	96%. . .	

DETD [0128] As shown in FIG. 4, SEQ ID No. 6, corresponding to cytokine inducible **CIITA** promoter IV, contains at least 3 potential cis-acting elements which could be involved in transcription regulation of a gene located. . .

DETD . . . GBP (Briken et al., 1995, Mol. Cell. Biol., 15, 975-982), we investigated the role of IRF-1 in the induction of **CIITA** by interferon gamma. RNAs from embryonic fibroblasts (EF) derived from wild-type (wt) and from IRF-1.sup.- mice (which do not express IRF-1) were compared for **CIITA** mRNA expression stimulation by interferon gamma. RNAse protection assays revealed that, in contrast to wild-type EF, interferon gamma induced **CIITA** mRNA expression was strongly reduced in IRF-1.sup.- EF. The same inhibition of interferon gamma stimulation was observed for GBP mRNA.. . .

DETD SEQUENCE CHARACTERISTICS:
LENGTH: 5463 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** gene of type I
SEQUENCE: 1
GTAAGTACTG TAACAGAGAC TAAATGCTAA GTAAGGCAGG CGTGGTGGCT CACACTTGTA 60
ATCCCAGTAC TTTGGAGGAC TGAGGCAAGA GGATCACTTG AGCCCAGAAT TCAAGACCAG 120
CCTGGGAAAC. . .

DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4564 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** gene of type II
SEQUENCE: 2
CCCGGGCGCC CCGCCTCAGT TTCCCCATCT ATAAAGTGGA GATGATAATA GCATTCAGAG 60
TCACTGATCT AAGGGCTCAG GGACACCATT CAGTGTAAGC CCCATACACT CCCTGCAAGA 120
GGAAGCTGGT. . .

DETD SEQUENCE CHARACTERISTICS:
LENGTH: 5105 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** gene of type IV
SEQUENCE: 3
GGGGAGAAGT CAGAGGTAAC CTTGCCCCCT CCCTCAATTC CAGATGAGGA AATTCAGGCC 60
TGAAAAGGGA AAGTGACCAC CTCAAAGTCT CATGCCTTGG AGGACCCAGC AGGAATCCAA 120
GACCTCTGAA. . .

DETD SEQUENCE CHARACTERISTICS:
LENGTH: 717 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** promoter of type I
SEQUENCE: 4

GTAAGTACTG TAACAGAGAC TAAATGCTAA GTAAGGCAGG CGTGGTGGCT CACACTTGTA 60
ATCCCAGTAC TTTGGAGGAC TGAGGCAAGA GGATCACTTG AGCCCAGAAT TCAAGACCAG 120
CCTGGGAAAC. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 133 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** promoter of type II
SEQUENCE: 5
CCCGGGCGCC CCGCCTCAGT TTCCCCATCT ATAAAGTGGA GATGATAATA GCATTCAGAG 60
TCACTGATCT AAGGGCTCAG GGACACCATT CAGTGTAAGC CCCATACACT CCCTGCAAGA 120
GGAAGCTGGT. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 664 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** promoter of type I
SEQUENCE: 6
GGGGAGAAGT CAGAGGTAAC CTTGCCCCCT CCCTCAATTC CAGATGAGGA AATTCAGGCC 60
TGAAAAGGGA AAGTGACCAC CTCAAAGTCT CATGCCTTGG AGGACCCAGC AGGAATCCAA 120
GACCTCTGAA. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4746 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** of type I
SEQUENCE: 7
CGTCCTGGTT TTCACTTCAT GTTTTGGATG CTGCATGCTG GGTGAGCGGA GATTCCAGGC 60
ACTGGCCAGG GCAGCTGCCC TGACTCCAAG GGCTGCCATG AACAACTTCC AGGCCATCCT 120
GACTCAGGTG AGAATGCTGC. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4431 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** de type II
SEQUENCE: 8
GACTCAGCCT TGAGGCTGGC GTCTGAGGCA ACCACAAGCC CAACGTGCAT GGTGGAAAGA 60
TGACTGCAGC TCACAGTGTG CCACCATGGA GTTGGGGCCC CTAGAAGGTG GCTACCTGGA 120
GCTTCTTAAC AGCGATGCTG. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4549 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** of type III
SEQUENCE: 9
TTAGTGATGA GGCTAGTGAT GAGGCTGTGT GCTTCTGAGC TGGGCATCCG AAGGCATCCT 60
TGGGGAAGCT GAGGGCACGA GGAGGGGCTG CCAGACTCCG GGAGCTGCTG CCTGGCTGGG 120
ATTCCTACAC AATGCGTTGC. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4441 base pairs

TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** of type IV
SEQUENCE: 10
CAGACTTGCC GCGGCCCCAG AGCTGGCGGG AGGGAGAGGC CACCAGCAGC GCGCGCGGGA 60
GCCCGGGGAA CAGCGGCAGC TCACAGTGTG CCACCATGGA GTTGGGGCCC CTAGAAGGTG 120
GCTACCTGGA GCTTCTTAAC. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4649 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** of type I
SEQUENCE: 11
ATGAACAACT TCCAGGCCAT CCTGACTCAG GTGAGAATGC TGCTCTCCAG CCATCAGCCC 60
AGCCTGGTGC AGGCCCTCTT GGACAACCTG CTGAAGGAGG ACCTCCTCTC CAGGGAATAC 120
CACTGCACTC TGCTCCATGA. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4346 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** of type II
SEQUENCE: 12
ATGGAGTTGG GGCCCCTAGA AGGTGGCTAC CTGGAGCTTC TTAACAGCGA TGCTGACCCC 60
CTGTGCCTCT ACCACTTCTA TGACCAGATG GACCTGGCTG GAGAAGAAGA GATTGAGCTC 120
TACTCAGAAC CCGACACAGA. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4418 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** of type III
SEQUENCE: 13
ATGCGTTGCC TGGCTCCACG CCCTGCTGGG TCCTACCTGT CAGAGCCCCA AGGCAGCTCA 60
CAGTGTGCCA CCATGGAGTT GGGGCCCCTA GAAGGTGGCT ACCTGGAGCT TCTTAACAGC 120
GATGCTGACC CCCTGTGCCT. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 4366 base pairs
TYPE: nucleic acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: DNA (genomic)
FEATURE:
NAME/KEY: **cIIta** of type IV
SEQUENCE: 14
GCAGCTCACA GTGTGCCACC ATGGAGTTGG GGCCCCTAGA AGGTGGCTAC CTGGAGCTTC 60
TTAACAGCGA TGCTGACCCC CTGTGCCTCT ACCACTTCTA TGACCAGATG GACCTGGCTG 120
GAGAAGAAGA GATTGAGCTC. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 1207 amino acids
TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
FEATURE:
NAME/KEY: **cIIta** of type I

SEQUENCE: 16
Met Asn Asn Phe Gln Ala Ile Leu Thr Gln Val Arg Met Leu Leu Ser. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 1106 amino acids
TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
FEATURE:
NAME/KEY: **cIIta** of type I
SEQUENCE: 17
Met Glu Leu Gly Pro Leu Glu Gly Gly Tyr Leu Glu Leu Leu Asn Ser. . .
DETD SEQUENCE CHARACTERISTICS:
LENGTH: 1130 amino acids
TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
FEATURE:
NAME/KEY: **cIIta**
SEQUENCE: 18
Met Arg Cys Leu Ala Pro Arg Pro Ala Gly Ser Tyr Leu Ser Glu Pro
1 5 10. . .
CLM What is claimed is:
1. Nucleic acid sequence which comprises all or part of a nucleic acid sequence of a **CIITA** gene and which is selected from the sequences SEQ ID No. 1, SEQ ID No. 2 and SEQ ID No.. . .
. . . in that it comprises all or part of a sequence selected from: a) a nucleic acid sequence which encodes a **CIITA** polypeptide which consists of the amino acids defined in accordance with SEQ ID No. 16, and its complementary sequence, b). . . SEQ ID No. 11 and their complementary sequences, c) a nucleic acid sequence which encodes an allelic variant of a **CIITA** polypeptide such as defined in a).

. . . according to claim 17, characterized in that the said gene of interest is selected from the genes which encode a **CIITA** factor or the .alpha. and .beta. chains of the HLA-DR, HLA-DQ and/or HLA-DP molecules.

31. Process for producing a **CIITA** polypeptide, in particular as defined in SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18 or SEQ. . .
. . . that it exhibits the same function of transactivating the expression of the genes encoding MHC class II molecules as a **CIITA** factor.

. . . claim 10, characterized in that it contains at least one mutation which affects the function or the expression of a **CIITA** factor.

. . . one of claims 1 to 10 of at least one mutation which affects the function or the expression of a **CIITA** factor is determined by analysing the said nucleic acid sequence and comparing with a wild-type sequence.

L3 ANSWER 16 OF 47 USPATFULL
ACCESSION NUMBER: 2002:265930 USPATFULL
TITLE: **CIITA**-interacting proteins and methods of use therefor
INVENTOR(S): Glimcher, Laurie H., West Newton, MA, UNITED STATES
Zhou, Hong, Wilmington, DE, UNITED STATES
PATENT ASSIGNEE(S): President and Fellows of Harvard College (U.S. corporation)

	NUMBER	KIND	DATE
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LEGAL REPRESENTATIVE: LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
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NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 2820
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **CIITA**-interacting proteins and methods of use therefor

AB Isolated nucleic acid molecules encoding a novel protein, CIP104, that interacts with **CIITA**, an MHC class II transcriptional activator, are disclosed. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression. . . . methods of modulating CIP104 activity in a cell, and methods for identifying agents that modulate an interaction between CIP104 and **CIITA**.

SUMM [0005] Activation of transcription of the MHC Class II genes has been shown to be dependent upon the transactivator **CIITA** (Steimle et al., 1993, Cell 75:135-146). **CIITA** does not function by directly binding DNA itself but rather by interacting with a conserved set of DNA binding proteins. . . . 4:167-178; Mach et al. (1996) Annu. Rev. Immunol. 14:301-331; Riley et al. (1995) Immunity 2:533-543). The transcriptional activation function of **CIITA** has been mapped to an amino terminal acidic domain (amino acids 26-137) (Zhou and Glimcher (1995) Cell 2:545-553). The defect in a subset of MHC Class II deficient patients has been shown to be a mutation in **CIITA**, thereby demonstrating the importance of **CIITA** in regulating MHC Class II gene transcription (Steimle et al., 1993, Cell 75:135-146; Bontron et al. (1997) Hum. Genet. 99:541-546; Steimle et al. (1996) Adv. ImmunoL 61:327-340). Given the critical role that **CIITA** plays in regulating MHC Class II gene expression, further information on how **CIITA** functions is of great interest.

SUMM [0006] This invention pertains to a protein that interacts with **CIITA** and enhances **CIITA**-regulated transciption from MHC class II gene promoters. A nucleic acid molecule encoding a protein that interacts with **CIITA**, termed **CIITA**-interacting protein 104 (also referred to herein as CIP104), has now been isolated and characterized. The CIP104-encoding nucleic acid was isolated based upon the ability of the encoded protein to interact with **CIITA** in a yeast two hybrid assay system. The nucleotide sequence of a cDNA encoding CIP104 and the predicted amino acid. . .

SUMM . . . an amino acid sequence that is homologous to the amino acid sequence of SEQ ID NO: 2 and interacts with **CIITA**. In yet another embodiment, the invention provides an isolated nucleic acid molecule which hybridizes under stringent conditions to a nucleic. . . encoding the amino acid sequence of SEQ ID NO: 2. Isolated nucleic acid molecules encoding CIP104 fusion proteins and isolated **antisense** nucleic acid molecules are also encompassed by the invention.

SUMM [0009] Still another aspect of the invention pertains to isolated **CIITA**-interacting proteins, or portions thereof. In one embodiment, the invention provides an isolated CIP104 protein, or a portion thereof that interacts with **CIITA**. In yet another embodiment, the invention provides an isolated protein which comprises an amino acid sequence homologous to the amino acid sequence of SEQ ID NO: 2 and that interacts with **CIITA**. CIP104 fusion proteins are also encompassed by the invention.

SUMM . . . that modulate the activity or expression of CIP104 and methods for identifying compounds that modulate an interaction between CIP104 and **CIITA**. Screening methods for identifying proteins that interact with CIP are also encompassed by the invention.

DRWD . . . reticulocyte lysate transcription/translation system.

pCI.cndot.CIP104 (as) represents a control expression vector in which the CIP104-coding sequences are oriented in the **antisense** orientation, which fails to direct expression of a protein. pCI represents the parental control expression vector, which lacks CIP104 coding sequences. pCMV.cndot.**CIITA** represents a **CIITA** expression vector, which directs expression of **CIITA** protein.

DRWD . . . of the human MHC class II DR.alpha. promoter, either in the absence (bars 1-4) or in presence (bars 5-8) of **CIITA**.

DRWD . . . of CIP104 on transactivation of the B7.1 promoter, either in the absence (bars 1-4) or in presence (bars 5-8) of **CIITA**.

DETD . . . invention pertains to a CITA Interacting Protein 104 (CIP104), a protein that interacts with the MHC class II transcriptional transactivator **CIITA**. A cDNA encoding CIP104 was isolated based upon the interaction of CIP104 with the interaction domain of **CIITA** using a two-hybrid interaction trap assay in yeast (see Example 1). Expression of CIP104 mRNA in various tissue has been. . . expression observed in thymus (see Example 2). Functional studies showed that CIP104 enhances transactivation of MHC class II promoters by **CIITA** (see Example 3).

DETD [0021] As used herein, the term "**CIITA**" is intended to refer to the human MHC Class II transcriptional regulatory protein having the amino acid sequence described in Steimle et al. (1993) Cell 75:135-146, as well as the equivalent protein in other species (e.g., mouse **CIITA**).

DETD [0028] As used herein, an "**antisense**.times. nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, e.g., complementary to. . . a double-stranded cDNA molecule, complementary to an mRNA sequence or complementary to the coding strand of a gene. Accordingly, an **antisense** nucleic acid can hydrogen bond to a sense nucleic acid.

DETD . . . term "biologically active portion of CIP104" is intended to include portions of CIP104 that retain the ability to interact with **CIITA**. The ability of portions of CIP104 to interact with **CIITA** can be determined in standard in vitro interaction assays, for example using a **CIITA** fusion protein that comprises the interaction domain of **CIITA** that interacts with CIP104. Nucleic acid fragments encoding biologically active portions of CIP104 can be prepared by isolating a portion. . . or peptide (e.g., by recombinant expression in a host cell) and assessing the ability of the portion to interact with **CIITA**, for example using a glutathione-S-transferase (GST)-**CIITA** fusion protein.

DETD . . . sequence of SEQ ID NO: 2) without altering the functional activity of CIP104, such as its ability to interact with **CIITA** or its ability to enhance transcription from MHC class II promoters, whereas an "essential" amino acid residue is required for. . .

DETD . . . amino acid sequence at least 60% homologous to the amino acid sequence of SEQ ID NO: 2 and interacts with **CIITA** or enhances transcription from MHC class II promoters. Preferably, the protein encoded by the nucleic acid molecule is at least. . .

DETD . . . at least 60% homologous to the nucleotide sequence of SEQ ID NO: 1 and encodes a protein that interacts with **CIITA** or enhances transcription from MHC class II promoters. Preferably, the nucleotide sequence is at least 70% hc.nologous to SEQ ID. . .

DETD [0051] An isolated nucleic acid molecule encoding a **CIITA** -interacting protein homologous to the protein of SEQ ID NO: 2 can be created by introducing one or more nucleotide substitutions,. . . coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for their ability to interact with **CIITA** (e.g., using a GST-**CIITA** fusion protein) to identify mutants that retain **CIITA**-interacting ability.

DETD . . . mutant protein can be expressed recombinantly in a host cell and the ability of the mutant protein to interact with **CIITA** can be determined using an in vitro interaction assay. For example, a recombinant CIP104 (e.g., a mutated or truncated form of SEQ ID NO: 2)

can be radiolabeled and incubated with a GST-**CIITA** fusion protein. Glutathione-sepharose beads are then added to the mixture to precipitate the CIP1 04-**CIITA**-GST complex, if such a complex is formed. After washing the beads to remove non-specific binding, the amount of radioactive protein. . . . amount of radioactive protein remaining in the eluate to thereby determine whether the mutant CIP104 is capable of interacting with **CIITA**.

DETD [0074] Another aspect of the invention pertains to isolated nucleic acid molecules that are **antisense** to the coding strand of a CIP104 mRNA or gene. An **antisense** nucleic acid of the invention can be complementary to an entire CIP104 coding strand, or to only a portion thereof. In one embodiment, an **antisense** nucleic acid molecule is **antisense** to a coding region of the coding strand of a nucleotide sequence encoding CIP104 (e.g., the coding region of SEQ ID NO: 1 comprises nucleotides 509-3343). In another embodiment, the **antisense** nucleic acid molecule is **antisense** to a noncoding region of the coding strand of a nucleotide sequence encoding CIP104. In certain embodiments, an **antisense** nucleic acid of the invention is at least 300, nucleotides in length. More preferably, the **antisense** nucleic acid is at least 400, 500, 600, 700, 800, 900 or 1000 nucleotides in length. In preferred embodiments, an **antisense** of the invention comprises at least 30 contiguous nucleotides of the noncoding strand of SEQ ID NO: 1, more preferably. .

DETD [0075] Given the coding strand sequences encoding CIP104 disclosed herein (e.g., SEQ ID NO: 1), **antisense** nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The **antisense** nucleic acid molecule may be complementary to the entire coding region of CIP104 mRNA, or alternatively can be an oligonucleotide which is **antisense** to only a portion of the coding or noncoding region of CIP104 mRNA. For example, the **antisense** oligonucleotide may be complementary to the region surrounding the translation start site of CIP104 mRNA. An **antisense** oligonucleotide can be, for example, about 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An **antisense** nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an **antisense** nucleic acid (e.g, an **antisense** oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the **antisense** and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the **antisense** nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an **antisense** orientation (i e., RNA transcribed from the inserted nucleic acid will be of an **antisense** orientation to a target nucleic acid of interest, described further in the following subsection).

DETD [0076] In another embodiment, an **antisense** nucleic acid of the invention is a **ribozyme**. **Ribozymes** are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an MRNA, to which they have a complementary region. A **ribozyme** having specificity for a CIP104-encoding nucleic acid can be designed based upon the nucleotide sequence of a CIP104 cDNA disclosed. . .

DETD . . . further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an **antisense** orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is **antisense** to CIP104 mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the **antisense** orientation can be chosen which direct the continuous expression of the

antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of **antisense** RNA. The **antisense** expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which **antisense** nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined. . . by the cell type into which the vecto is introduced. For a discussion of the regulation of gene expression using **antisense** genes see Weintraub, H. et al., **Antisense** RNA as a molecular tool for genetic analysis, Reviews--Trends in Genetics, Vol. 1(1) 1986.

DETD . . . acid sequence at least 60% homologous to the amino acid sequence of SEQ ID NO: 2 and that interacts with **CIITA** or enhances transcription from MHC class II promoters. Preferably, the protein is at least 70% homologous to SEQ ID NO:. . .

DETD . . . portions of the CIP104 protein. For example, the invention further encompasses a portion of a CIP104 protein that interacts with **CIITA**. As demonstrated in the examples, CIP104 protein interacts with the interation domain of **CIITA** (about amino acid positions 134 to 317 of **CIITA**). An in vitro interaction assay (such as that described above in subsection I utilizing a GST-**CIITA** fusion protein comprising the interaction domain of **CIITA**) can be used to determine the ability of CIP104 peptide fragments to interact with the interaction domian of **CIITA** to thereby identify peptide fragments that interact with **CIITA**.

DETD . . . a preferred embodiment, the method identifies compounds that modulate the activity of CIP104 by modulating the interaction between CIP104 and **CIITA**. Accordingly, in a preferred embodiment of the above-described method, the indicator composition comprises a CIP104 protein and a **CIITA** protein and the effect of the test compound on the activity of the CIP104 protein is determined by determining the degree of interaction between the CIP104 protein and the **CIITA** protein the presence and absence of the test compound. The method can be carried out either in vitro or in vivo in cells. For example, for an in vitro assay, recombinant CIP104 and recombinant **CIITA** can be combined in the presence and absence of a test compound and the degree of interaction between CIP104 and **CIITA** in the presence and absence of the test compound can be determined by standard methods known in the art (e.g., by evaluating the amount of CIP104 co-precipitated with **CIITA** in the presence and absence of the test compound or by labeling one of the two proteins and evaluating the. . . with the nonlabeled protein in the presence and absence of the test compound). For an in vitro assay, CIP104 and **CIITA** can be expressed in a host cell that also contains a reporter gene whose expression is dependent upon interaction of CIP104 and **CIITA**. The effect of a test compound on the interaction between CIP104 and **CIITA** in the cell can then be evaluated by determining the level of expression of the reporter gene in the presence. . . CIP104 (described further in Example 1) can be adapted to identifying test compounds that modulate the interaction of CIP104 with **CIITA**.

DETD . . . preferred embodiment, the method identifies compounds that modulate the activity of CIP104 by modulating the ability of CIP104 to enhance **CIITA**-regulated gene transcription. Accordingly, in another preferred embodiment of the above-described method, the indicator composition is a cell comprising a CIP104 protein, a **CIITA** protein and a reporter gene responsive to **CIITA** and the effect of the test compound on the activity of the CIP104 protein is determined by determining the level. . . expression of the reporter gene in the presence and absence of the test compound. Preferably, the reporter gene responsive to **CIITA** comprises a major histocompatibility complex (MHC) class II gene promoter. A preferred assay system for examining the effect of test compounds on CIP104 enhancement of **CIITA**-regulated gene expression is

described further in Example 3, in which a host cell is transfected with (i) an expression vector encoding CIP104, (ii) an expression vector encoding **CIITA** and (ii) a DR.alpha.-CAT reporter gene construct. The level of CAT activity in the host cell in the presence and absence of a test compound can be used to determine the effect of the test compound on CIP104-enhanced **CIITA**-regulated MHC class II gene expression.

DETD [0128] Preferred methods of the invention for identifying agents that modulate the interaction between CIP104 and **CIITA** can comprise, for example,

DETD [0130] (i) CIP104, or an **CIITA**-interacting portion thereof; and

DETD [0131] (ii) an **CIITA**, or a CIP104-interacting portion thereof;

DETD [0133] c) identifying an agent that modulates an interaction between CIP104 and **CIITA**.

DETD [0134] Isolated CIP104 and/or **CIITA** may be used in the method, or, alternatively, only portions of CIP104 and/or **CIITA** may be used. For example, an isolated interaction domain of **CIITA** can be used as the CIP104-interacting portion of **CIITA**. Likewise, a portion of CIP104 capable of binding to the interaction domain of **CIITA** may be used. In a preferred embodiment, one or both of (i) and (ii) are fusion proteins, such as GST. . . . non-labeled protein. The assay can be used to identify agents that either stimulate or inhibit the interaction between CIP104 and **CIITA**. An agent that stimulates the interaction between CIP104 and **CIITA** is identified based upon its ability to increase the degree of interaction between (i) and (ii) as compared to the degree of interaction in the absence of the agent, whereas an agent that inhibits the interaction between CIP104 and **CIITA** is identified based upon its ability to decrease the degree of interaction between (i) and (ii) as compared to the. . . domain-ligand interactions as described in U.S. Pat. No. 5,352,660 by Pawson can be adapted to identifying agents that modulate the CIP104/**CIITA** interactions.

DETD . . . An inhibitory agent may function, for example, by directly inhibiting CIP104 activity or by inhibiting an interaction between CIP104 and **CIITA**. In another embodiment, the agent stimulates CIP104 activity. A stimulatory agent may function, for example, by directly stimulating CIP104 activity or by promoting an interaction between CIP104 and **CIITA**.

DETD . . . encodes the protein or to a second protein with which the first protein normally interacts (e.g., molecules that bind to **CIITA** to thereby inhibit the interaction between CIP104 and **CIITA**). Examples of intracellular binding molecules, described in further detail below, include **antisense** CIP104 nucleic acid molecules (e.g., to inhibit translation of CIP104 mRNA), intracellular anti-CIP104 antibodies (e.g., to inhibit the activity of. . .

DETD [0159] In one embodiment, an inhibitory agent of the invention is an **antisense** nucleic acid molecule that is complementary to a gene encoding CIP104, or to a portion of said gene, or a recombinant expression vector encoding said **antisense** nucleic acid molecule. The use of **antisense** nucleic acids to downregulate the expression of a particular protein in a cell is well known in the art (see e.g., Weintraub, H. et al., **Antisense** RNA as a molecular tool for genetic analysis, Reviews--Trends in Genetics, Vol. 1(1) 1986; Askari, F. K. and McDonnell, W.. . . . (1995) Cancer Gene Ther. 2:47-59; Rossi, J. J. (1995) Br. Med. Bull. 51:217-225; Wagner, R. W. (1994) Nature 372:333-335). An **antisense** nucleic acid molecule comprises a nucleotide sequence that is complementary to the coding strand of another nucleic acid molecule (e.g.,. . . . an mRNA sequence) and accordingly is capable of hydrogen bonding to the coding strand of the other nucleic acid molecule. **Antisense** sequences complementary to a sequence of an mRNA can be complementary to a sequence found in the coding region of. . . region and an untranslated region (e.g., at the junction of the 5' untranslated region

and the coding region). Furthermore, an **antisense** nucleic acid can be complementary in sequence to a regulatory region of the gene encoding the mRNA, for instance a transcription initiation sequence or regulatory element. Preferably, an **antisense** nucleic acid is designed so as to be complementary to a region preceding or spanning the initiation codon on the coding strand or in the 3' untranslated region of an mRNA. An **antisense** nucleic acid for inhibiting the expression of CIP104 protein in a cell can be designed based upon the nucleotide sequence. . .

DETD [0160] An **antisense** nucleic acid can exist in a variety of different forms. For example, the **antisense** nucleic acid can be an oligonucleotide that is complementary to only a portion of a CIP104 gene. An **antisense** oligonucleotides can be constructed using chemical synthesis procedures known in the art. An **antisense** oligonucleotide can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the **antisense** and sense nucleic acids, e.g. phosphorothioate derivatives and acridine substituted nucleotides can be used. To inhibit CIP104 expression in cells in culture, one or more **antisense** oligonucleotides can be added to cells in culture media, typically at about 200 .mu.g oligonucleotide/ml.

DETD [0161] Alternatively, an **antisense** nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an **antisense** orientation (i.e., nucleic acid transcribed from the inserted nucleic acid will be of an **antisense** orientation to a target nucleic acid of interest). Regulatory sequences operatively linked to a nucleic acid cloned in the **antisense** orientation can be chosen which direct the expression of the **antisense** RNA molecule in a cell of interest, for instance promoters and/or enhancers or other regulatory sequences can be chosen which direct constitutive, tissue specific or inducible expression of **antisense** RNA. For example, for inducible expression of **antisense** RNA, an inducible eukaryotic regulatory system, such as the Tet system (e.g., as described in Gossen, M. and Bujard, H.. . . et al. (1995) Science 268:1766-1769; PCT Publication No. WO 94/29442; and PCT Publication No. WO 96/01313) can be used. The **antisense** expression vector is prepared as described above for recombinant expression vectors, except that the cDNA (or portion thereof) is cloned into the vector in the **antisense** orientation. The **antisense** expression vector can be in the form of, for example, a recombinant plasmid, phagemid or attenuated virus. The **antisense** expression vector is introduced into cells using a standard transfection technique, as described above for recombinant expression vectors.

DETD [0162] In another embodiment, an **antisense** nucleic acid for use as an inhibitory agent is a **ribozyme**. **Ribozymes** are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region (for reviews on **ribozymes** see e.g., Ohkawa, J. et al. (1995) J. Biochem. 118:251-258; Sigurdsson, S. T. and Eckstein, F. (1995) Trends Biotechnol. 13:286-289; Rossi, J. J. (1995) Trends Biotechnol 13:301-306; Kiehntopf, M et al. (1995) J. Mol. Med. 73:65-71). A **ribozyme** having specificity for CIP104 mRNA can be designed based upon the nucleotide sequence of the CIP104 cDNA. For example, a. . .

DETD . . . activity of a CIP104 protein are chemical compounds that directly inhibit CIP104 activity or inhibit the interaction between CIP104 and **CIITA**. Such compounds can be identified using screening assays that select for such compounds, as described in detail above.

DETD . . . negative-inhibitor. A dominant negative inhibitor can be a form of a CIP104 protein that retains the ability to interact with **CIITA** but that lacks one or more other functional activities

such that the dominant negative form of CIP104 acts to inhibit the ability of the CIP104/**CIITA** complex to activate transcription. This dominant negative form of a CIP104 protein may be, for example, a mutated form of CIP104 in which the region of the protein that interacts with **CIITA** is conserved but in which one or more amino acid residues elsewhere in the protein are mutated. Such dominant negative. . . a cell to allow for expression ofthe mutated CIP104 protein. The ability of the mutant CIP104 protein to interact with **CIITA** can be assessed using standard in vitro interaction assays. The effect of the mutant CIP104 protein on transcriptional activation can. . . assessing the effect of the mutant CIP104 protein in transcription of the reporter gene. The indicator cells should express endogenous **CIITA** or should be transfected to express **CIITA**. A mutant form of CIP104 that retains the ability to interact with CIP104 but that interferes with transcriptional activation from MHC class II promoters when co-expressed in cells with **CIITA** can be selected as a dominant negative inhibitor of CIP104 activity.

DETD . . . be used to inhibit the activity of a CIP104 protein are chemical compounds that inhibit the interaction between CIP104 and **CIITA**. Such compounds can be identified using screening assays that select for such compounds, as described in detail above.

DETD . . . activity in cells, such as compounds that directly stimulate CIP104 protein and compounds that promote the interaction between CIP104 and **CIITA**. Such compounds can be identified using screening assays that select for such compounds, as described in detail above.

DETD [0173] For stimulatory or inhibitory agents that comprise nucleic acids (including recombinant expression vectors encoding CIP104 protein, **antisense** RNA, intracellular antibodies or dominant negative inhibitors), the agents can be introduced into cells of the subject using methods known. . .

DETD [0182] A modulatory agent, such as a chemical compound that modulates the CIP104/**CIITA** interaction, can be administered to a subject as a pharmaceutical composition. Such compositions typically comprise the modulatory agent and a. . .

DETD . . . defective MHC class II gene expression. In a preferred embodiment, MHC class II deficiency syndrome caused by a mutation in **CIITA** is treated by providing a normal **CIITA** to the patients (e.g., by gene therapy with a **CIITA** gene) in combination with upregulating CIP104 activity (e.g., by gene therapy with a CIP104 gene).

DETD [0191] A yeast two-hybrid interaction trap assay was used to isolate proteins that could directly bind to the MHC-transactivator protein **CIITA**. A **CIITA**-Gal4 fusion protein was prepared for use as the "bait" in the yeast two-hybrid assay by cloning a fragment of human **CIITA** that had an internal deletion of amino acid residues 21 to 134 (referred to herein as **CIITA**..DELTA.AD) into the vector pEG202 (Gyuris, J. et al. (1993) Cell 75:791-803) to thereby create an in-frame **CIITA**..DELTA.AD-Gal4 fusion. The **CIITA**..DELTA.AD fragment lacks the transcriptional activation domain of **CIITA** (at about residues 21-134) but retains a proline-serine-threonine (P-S-T) rich region at about residues 135-292. This bait was used to. . .

DETD . . . a protein of 945 amino acids having a predicted molecular weight of approximately 104 kD. The encoded protein was termed **CIITA**-Interacting Protein 104 (CIP104). Additional characterization demonstrated that CIP104 was able to interact with a **CIITA** in which the activation domain had been removed (i.e., the **CIITA**..DELTA.AD fragment used to isolate CIP104) but was unable to interact with a fragment of **CIITA** in which both the activation domain and the P-S-T region had been removed. Accordingly, these experiments demonstrate that the P-S-T region of **CIITA** is necessary for binding to CIP104.

DETD . . . protein of the expected molecular weight. In contrast, a control vector in which the CIP104 cDNA was cloned in the **antisense** orientation, pCI.cndot.CIP104 (as), did not result in

protein production. The parental control vector, pCI, similarly did not direct protein expression. A **CIITA** expression vector, pCMV.cndot.**CIITA**, directed expression of a protein of the expected molecular weight.

DETD . . . (i) a DR.alpha. promoter-reporter gene construct (DR.alpha.-CAT) (5 .mu.g) or (ii) both a DR.mu.promoter-reporter gene construct (5 .mu.g) and a **CIITA** expression vector (1 .mu.g). The total amount of DNA transfected into each cell was brought to 26 .mu.g using control vector DNA. The expression vector in which the CIP104 cDNA was cloned in the **antisense** orientation (pCI.cndot.CIP104 (as)) served as a control. The results of these studies are summarized in the graph of FIG. 3, which demonstrates that CIP104 alone (i.e., in the absence of **CIITA**) did not significantly stimulate expression of the DR.beta.-CAT reporter gene (see bars 1-4 of FIG. 3). In contrast, when CIP104 was coexpressed with **CIITA**, transactivation of the DR.beta.-CAT reporter gene was upregulated as compared to when **CIITA** was expressed alone (compare lane 5 of FIG. 3 with lanes 6-8). This effect of CIP104 was dose-dependent, with 20 .mu.g of CIP104 stimulating **CIITA**-mediated DR.beta.-CAT expression approximately 30-fold as compared to **CIITA** alone. No stimulation of **CIITA**-mediated DR.beta.-CAT expression was observed with the pCI.cndot.CIP104 (as) **antisense** control vector. These experiments demonstrate that CIP104 can potentiate the transcriptional activation ability of **CIITA** for MHC class II promoters.

DETD . . . results with the DR.beta.-CAT reporter gene, no effect on transcription of the B7.1-CAT reporter gene was observed when CIP104 and **CIITA** were coexpressed (see lanes 4-8). Moreover, CIP104 alone did not significantly stimulate B7.1-CAT expression. These results indicate that the synergistic of CIP104 and **CIITA** was not observed with a non-MHC class II promoter.

CLM What is claimed is:

. . . acid sequence at least 60% homologous to the amino acid sequence of SEQ ID NO: 2 and (ii) interacts with **CIITA** or enhances transcription from an MHC class II promoter.

. . . to the nucleotide sequence of SEQ ID NO: 1, wherein the nucleic acid molecule encodes a protein that interacts with **CIITA** or enhances transcription from an MHC class II promoter.

. . . acid sequence at least 60% homologous to the amino acid sequence of SEQ ID NO: 2 and (ii) interacts with **CIITA** or enhances transcription from an MHC class II promoter.

. . . 40. The method of claim 38, wherein the agent is a nucleic acid molecule having a nucleotide sequence that is **antisense** to the coding strand of a CIP104 mRNA or a CIP104 gene.

42. The method of claim 41, wherein: the indicator composition comprises a CIP104 protein and a **CIITA** protein;and the effect of the test compound on the activity of the CIP104 protein is determined by determining the degree of interaction between the CIP104 protein and the **CIITA** protein the presence and absence of the test compound.

43. The method of claim 41, wherein: the indicator composition is a cell comprising a CIP104 protein, a **CIITA** protein and a reporter gene responsive to **CIITA**; and the effect of the test compound on the activity of the CIP104 protein is determined by determining the level. . .

44. The method of claim 43, wherein the reporter gene responsive to **CIITA** comprises a major histocompatibility complex (MHC) class II gene promoter.

L3 ANSWER 17 OF 47 USPATFULL

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TITLE: IMMUNE ACTIVATION BY DOUBLE-STRANDED POLYNUCLEOTIDES

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EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Page(s)
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Class II RNA expression than methimazole; (b) inhibit the action of IFN and abnormal MHC expression by acting on the **CIITA** /Y-box regulatory system; and (c) exhibit therapeutic activities in vivo. Specifically they inhibit development of SLE in the (NZBxNZW)F.sub.1 mouse model. . .

SUMM . . . 871-878 (1992); V. Montani, et al., Endocrinology 139: 290-302 (1998)). Also, it has been shown that MMI decreases expression of **CIITA** increased Class II expression and this appears to be related to the action of MMI to enhance Y box protein. . .

SUMM . . . and in inhibiting IFN-induced Class II RNA expression than methimazole; (b) inhibit the action of IFN by acting on the **CIITA**/Y-box regulatory system; (c) may be significantly more soluble than methimazole, leading to significant formulation flexibility and advantages; (d) have less. . .

DETD . . . than Class II; .gamma.IFN increases Class II more than Class I. .gamma.IFN action is mediated by the Class II transactivator (**CIITA**); DNA does not similarly induce **CIITA**. Rather the DNA effect appears to be mediated by activation of STAT 1, STAT3, MAPK and NF-.gamma.B, as well as. . .

DETD . . . (PGC Science, Frederick, Md.), and subcloned into a pBluescript SK(+) vector at the same restriction site. The probe for rat **CIITA** is a cloned rat Type III **CIITA** cDNA fragment in pcDNA3 (K. Suzuki et al., manuscript in preparation). EcoRI is used to release a 4098 bp fragment. . .

DETD [0198] .gamma.IFN-increased MHC gene expression is mediated by several IFN-inducible genes, including the Class II transactivator (**CIITA**), RFX5, and the interferon regulatory factor-1 (IRF-1) (B. Mach, et al. Annu. Rev. Immunol. 14: 301-331 (1996); R. M. Ten,. . . (1993)). All three of these genes are induced by .gamma.IFN in this system (FIG. 3). The effect of dsDNA on **CIITA** RNA levels is, however, very different from .gamma.IFN, both as a function of time and level (FIG. 3). The effect. . .

DETD . . . on LMP2, TAP-1, invariant chain (Ii), HLA-DM.beta., and B7 are more like dsDNA than .gamma.IFN. Its effect on IRF-1 and **CIITA** , however, appears to be more a mixture of the effects of dsDNA and .gamma.IFN, as a function of both level. . .

DETD . . . Chain Reactions (RT-PCR), the MHC class II DNA probe used a sense primer having the nucleotide sequence, 5'-AGCAAGCCAGTCACAGAAGG-3', and an **antisense** primer with the sequence, 5'-GATTCGACTTGGAAGATGCC-3' (SEQ ID No: 19) which amplified a 546 bp product, from between 74 and 619. . . Contamination of genomic DNA in total RNA preparations was tested using PCR primers which detect an

intronic sequence of rat **CIITA** genome DNA (M. Pietrarelli et al., manuscript in preparation).

DETD . . . Contamination of genomic DNA in total RNA preparations was tested using PCR primers which detect an intronic sequence of rat **CIITA** genomic DNA (Pietrarelli, et al., manuscript in preparation).

DETD . . . (PGC Science, Frederick, Md.), and subcloned into a pBluescript SK(+) vector at the same restriction site. The probe for rat **CIITA** is a cloned rat Type III **CIITA** cDNA fragment in pcDNA3 (K. Suzuki et al., manuscript in preparation). EcoRI is used to release a 4098 bp fragment. . .

DETD . . . the cis elements with which they interact, and the coregulators which affect both, for example the Y box transcription factors, **CIITA**, and the CRE, are common factors or motifs in each. The resultant bystander activation of T cells leads to cytokine. . .

CLM What is claimed is:

. . . the gene or gene product is selected from the group consisting of TAP-1, TAP-2, a proteosome subunit, HLA-DM, invariant chain, **CIITA**, RFX5, B7 costimulatory molecule, PKR, IFN-beta, MAP Kinase, NF-KB, JAK, and a STAT.

L3 ANSWER 18 OF 47 USPATFULL

ACCESSION NUMBER:	2002:251947 USPATFULL		
TITLE:	Phospholipid Scramblases and methods of use thereof		
INVENTOR(S):	Sims, Peter J., Del Mar, CA, UNITED STATES Wiedmer, Therese, Del Mar, CA, UNITED STATES Silverman, Robert H., Beachwood, OH, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002137905	A1	20020926
APPLICATION INFO.:	US 2001-823847	A1	20010330 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2000-193939P		20000331 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Lisa A. Haile, Ph.D., Gray Cary Ware & Freidenrich LLP, 4365 Executive Drive, Suite 1600, San Diego, CA, 92121-2189		
NUMBER OF CLAIMS:	58		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	14 Drawing Page(s)		
LINE COUNT:	3514		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . For example, Phospholipid Scramblase polynucleotides may be subjected to site-directed mutagenesis. The polynucleotide sequence for Phospholipid Scramblase polypeptide also includes **antisense** sequences. The polynucleotides of the invention include sequences that are degenerate as a result of the genetic code. There are. . .

DETD . . . the other hand, IFN-.gamma. possesses unique immune system functions by activating macrophages and inducing MHC class II through transcription factor **CIITA**.

DETD . . . use in allele specific hybridization screening or PCR amplification techniques, subsets of the Phospholipid Scramblase sequences, including both sense and **antisense** sequences, and both normal and mutant sequences, as well as intronic, exonic and untranslated sequences, are provided. Such sequences may. . .

DETD . . . or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the **antisense** strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those. . .

DETD . . . and then incorporated into the genome. The transgenes of the invention include DNA sequences that encode Phospholipid Scramblase polypeptide-sense and **antisense** polynucleotides, which may be expressed in a transgenic non-human animal. The term "transgenic" as used herein additionally includes any organism. . .

DETD . . . kit from Boehringer Mannheim to a specific activity .gtoreq.1.times.10.sup.9 dpm/.mu.g. Due to non-specific hybridization of the cDNA probe, an RNA **antisense** probe was designed for HuPLSCR3. A PCR product of the 3' untranslated region of HuPLSCR3 was prepared using the forward. . . sequence (5'-AATTTAATACGACTCACTATAGGG-3') at the 5' end. The PCR product was purified using the Qiaquick PCR purification kit (Qiagen). A .sup.32P-labeled **antisense** RNA probe was prepared using 50 ng of the PCR product as template in T7 transcription reaction with .alpha.-.sup.32P-UTP (800. . . with 100 .mu.g/ml denatured salmon sperm DNA and 50 .mu.g/ml yeast RNA and hybridized in the same buffer containing .sup.32P-labeled **antisense** RNA probe (2.times.10.sup.6 cpm/ml) at 68.degree. C. for 18 hours. The blots were washed at a final stringency of 0.1.times.. . .

L3 ANSWER 19 OF 47 USPATFULL

ACCESSION NUMBER:	2002:179280 USPATFULL
TITLE:	Clinically intelligent diagnostic devices and mehtods
INVENTOR(S):	Jacobs, Alice A., Boston, MA, UNITED STATES Gupta, Vineet, Brookline, MA, UNITED STATES Nikolic, Boris, Charlestown, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002095073	A1	20020718	
APPLICATION INFO.:	US 2001-996056	A1	20011127	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-253284P	20001127	(60)
	US 2001-287994P	20010501	(60)
	US 2001-308870P	20010730	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	J. PETER FASSE, Fish & Richardson P.C., 225 Franklin Street, Boston, MA, 02110-2804
NUMBER OF CLAIMS:	34
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	38 Drawing Page(s)
LINE COUNT:	2940

SUMM . . . based on ATPase, kinesin, kinesin related proteins, myosin, DNA Helicase, DNA Sliding clamps, nucleic acid based rotaxanes and Pseudo-rotaxanes, circular **triplex** forming oligonucleotides (CTFO), duplex DNA; as well as chimeras and derivatives of such proteins and nucleic acids. The protrusions or. . .

DETD . . . small molecules, such as MGBs), or a combination of both. XNA probes usually bind to single-stranded nucleic acids, except for **triplex** forming oligos that bind duplexes. Thus, an optional denaturation step can be involved. Preferred probes are based on DNA oligonucleotides. . .

DETD . . . al., The EMBO Journal, 18(18):5131-5144, 1999); nucleic acid based rotaxanes and Pseudo-rotaxanes (Ryan et al., Chemistry and Biology, 1998); circular **triplex** forming oligonucleotide (CTFO) and duplex DNA (Rehman et al., 1999); as well as chimeras and derivatives of such proteins and. . .

DETD . . . signaling--gammac; Jak3; IL-2; IL-2Ra; and IL-7Ra; B) SCID associated with TCR related defects--CD3g; CD3e; and ZAP70; C) HLA class II deficiency--**CIITA**; RFX5; and RFXB; D) HLA class I deficiency (bare leukocyte syndrome)--TAP1 and TAP2; E) Immunodeficiency associated with defects in enzymes. . .

L3 ANSWER 20 OF 47 USPATFULL
ACCESSION NUMBER: 2002:55155 USPATFULL
TITLE: Human single nucleotide polymorphisms
INVENTOR(S): Cargill, Michele, Gaithersburg, MD, UNITED STATES
Ireland, James S., Gaithersburg, MD, UNITED STATES
Lander, Eric S., Cambridge, MA, UNITED STATES
PATENT ASSIGNEE(S): Whitehead Institute for Biomedical Research, Cambridge, MA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002032319	A1	20020314
APPLICATION INFO.:	US 2001-801274	A1	20010307 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-187510P	20000307 (60)
	US 2000-206129P	20000522 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON BROOK SMITH AND REYNOLDS, P.C., TWO MILITIA DR, LEXINGTON, MA, 02421-4799
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 8981
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . C,

G3177a1	WIAF-17539	HT27779	774	90 kD	ZNF174, zinc finger protein
		TGGACCCCAAGAGGC[G/T]CTCTCCCAGCTCCGA			
	S G	T	A	A	
G3182a5	WIAF-17541	HT2783	248	174	**MHC2TA**, MHC class II
		AGCGATGCTGACCCC[C/G]TGTGCCTCTACCACT			
	M C	G	L	V	
G3182a6	WIAF-17542	HT2783	340	transactivator	**MHC2TA**, MHC class II
		AGACACCATCAACTG[C/T]GACCAGTTCAGCAGG			
	S C	T	C	C	
G3182a7	WIAF-17543	HT2783	1301	transactivator	**MHC2TA**, MHC class II
		CAGCTGGCCCAAGGA[G/A]GCCTGGCTGAGGTGC			
	M G	A	G	S	
G3182a8	WIAF-17544	HT2783	2088	transactivator	**MHC2TA**, MHC class II
		CCCCCGGGGCCCTGG[C/G]AGAGCTGGCCAAGCT			
	M C	G	A	G	
G3182a9	WIAF-17545	HT2783	2187	transactivator	**MHC2TA**, MHC class II
		GGACCTGGGCGATGG[C/A]CAAAGGCTTAGTCCA			
	M C	A	A	D	
G3182a10	WIAF-17546	HT2783	2509	transactivator	**MHC2TA**, MHC class II
		GAAGCGGCTGCAGCC[G/A]GGGACACTGCGGGCG			
	S G	A	P	P	
G3182a11	WIAF-17547	HT2783	2680	transactivator	**MHC2TA**, MHC class II
		GGCCTTGGAGGCGGC[G/A]GGCCAAGACTTCTCC			
	S G	A	A	A	
G3182a12	WIAF-17548	HT2783	3286	transactivator	**MHC2TA**, MHC class II
		CAATAACTGCATCTG[C/T]GACGTGGGAGCCGAG			
	S C	T	C	C	

G3182a13 WIAF-17549 HT2783 3667 **MHC2TA**, MHC class II GGTTGGCCCCTGCCC[G/A]GCTGCGGAATGAACC
-- G A

transactivator

G3183a2 WI-18169 HT27861 1027 zinc finger protein C2H2-150, GCGGGAGCGGGGTGG[G/T]CTGGCCCTGGAGCCC
S G T G. . .

DETD . . . WIAF-17670 HT1848 1045 ERCC1, excision repair cross ACCCTGATGACCCCA[G/C]CTGCCAAGGAAACCC
-- G C

complementing rodent

repair

deficiency,

complementation

group 1 (includes

overlapping

antisense

sequence)

G961a6 WIAF-17595 U95019 1324 CACNB2, calcium channel, ATCTCGCTTGCCAAA[C/T]GCTCGGTATTAAACA
C T R C M

voltage-dependent, beta 2 subunit

G962a5 WIAF-17595 U95020 930. . .

L3 ANSWER 21 OF 47 USPATFULL

ACCESSION NUMBER: 2002:48291 USPATFULL
TITLE: NIP45 HUMAN HOMOLOG
INVENTOR(S): ZHOU, HONG, WILMINGTON, DE, UNITED STATES
ZHOAO, JIUQIAO, HOCKESSIN, DE, UNITED STATES
LIU, DERONG, WILMINGTON, DE, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002028482	A1	20020307	
APPLICATION INFO.:	US 1998-175254	A1	19981020	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1997-22388	19971024

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LIPD DEPT (FOC 1 S/E), ZENECA INC, 1800 CONCORD PIKE, P O BOX 5437, WILMINGTON, DE, 198505437

NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 2356
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0033] The invention is further directed to an **antisense** poynucleotide molecule comprising substantially the complement of SEQ ID NO:2 or a biologically-effective portion thereof as well as a method for inhibiting the expression of a human NIP45 trans-activator biological molecule comprising administering an effective amount of the **antisense** molecule.

SUMM [0034] The invention is further directed to an **antisense** poynucleotide molecule comprising substantially the complement of SEQ ID NO:2 or a biologically-effective portion thereof as well as a method for modulating the expression of IL-4 in a cell comprising administering an effective amount of the **antisense** molecule.

DETD . . . to DNA or RNA of genomic or synthetic origin which may be double-stranded or single-stranded whether representing the sense or **antisense** strand. Similarly, amino acid and/or residue sequence as used herein refers to peptide or protein sequences or portions thereof.

DETD . . . as used herein refers to the direct administration of nucleic acid constructs which encode reagents (e.g., hNIP45, modulator compound molecule, **antisense** molecule, antibody molecule) of the present invention or fragments thereof; and the direct administration of reagents of the present invention. . .

DETD [0089] The nucleic acid sequence also provides for the design of **antisense** molecules useful in downregulating, diminishing, or eliminating expression of the genomic nucleotide sequence in cells including leukocytes, endothelial cells, and. . .

DETD . . . to pharmaceutical compounds and compositions comprising the human NIP45 molecule substantially as depicted in SEQ ID NO:3, or fragments thereof, **antisense** molecules capable of disrupting expression of the naturally occurring gene, and agonists, antibodies, antagonists or inhibitors of the native transcriptional. . .

DETD [0150] **Antisense** Molecules

DETD [0152] To enable methods of down-regulating expression of the hNIP45 of the present invention in mammalian cells, an example **antisense** expression construct containing the complement DNA sequence to the sequence substantially as depicted in SEQ ID NO:2 can be readily. . . be less effective in hybridizing the mRNA transcripts because of a "read-through" phenomenon whereby the ribosome appears to unravel the **antisense**/sense duplex to permit translation of the message. Oligonucleotides which are complementary to and hybridizable with any portion of the novel. . .

DETD [0153] Nucleotide sequences that are complementary to the novel hNIP45 polypeptide encoding polynucleotide sequence can be synthesized for **antisense** therapy. These **antisense** molecules may be DNA, stable derivatives of DNA such as phosphorothioates or methylphosphonates, RNA, stable derivatives of RNA such as. . . Pat. No. 5,652,356, Inverted Chimeric and Hybrid Oligonucleotides, issued Jul. 29, 1997, which describe the synthesis and effect of physiologically-stable **antisense** molecules, are incorporated by reference. Human NIP45 **antisense** molecules may be introduced into cells by microinjection, liposome encapsulation or by expression from vectors harboring the **antisense** sequence. **Antisense** therapy may be particularly useful for the treatment of diseases where it is beneficial to modulate IL-4 gene expression.

DETD . . . polypeptide of the present invention may be delivered to the cells of target organs in this manner. Conversely, hNIP45 polypeptide **antisense** gene therapy may be used to modulate the expression of the polypeptide in the cells of target organs and hence. . .

DETD [0157] The nucleic acid sequence, oligonucleotides, fragments, portions or **antisense** molecules thereof, may be used in diagnostic assays of body fluids or biopsied tissues to detect the expression level of. . .

DETD [0160] Pharmaceutically useful compositions comprising sequences pertaing to the novel human NIP45 polypeptide DNA, RNA, **antisense** sequences, or the human oNIP45 polypeptide itself, or variants and analogs which have the human NIP45 biological activity or otherwise. . .

DETD . . . the protected reverse yeast 2-hybrid system. The compound toxicity was found to cause high false positive rate in the previous **C2TA** HTS experiments.

Assay type:	Protein-protein interaction inhibition.
Test concentration:	10.sup.-4M
DMSO concentration (final):	1.0%
Assay temperature:	30.degree. C.
Incubation time:	24 hours for induced. . .

CLM What is claimed is:

4. An **antisense** molecule comprising the complement of the polynucleotide of claim 2 or a biologically-effective portion thereof.

. . . 26. A method for inhibiting the expression of a NIP45 in a cell

comprising administering an effective amount of an **antisense** molecule according to claim 4 to said cell.

27. A method for modulating the expression of IL-4 in a cell comprising administering an effective amount of an **antisense** molecule according to claim 4 to said cell.

L3 ANSWER 22 OF 47 USPATFULL

ACCESSION NUMBER:	2002:43671 USPATFULL
TITLE:	49 human secreted proteins
INVENTOR(S):	Moore, Paul A., Germantown, MD, UNITED STATES Ruben, Steven M., Olney, MD, UNITED STATES Olsen, Henrik S., Gaithersburg, MD, UNITED STATES Shi, Yanggu, Gaithersburg, MD, UNITED STATES Rosen, Craig A., Laytonsville, MD, UNITED STATES Florence, Kimberly A., Rockville, MD, UNITED STATES Soppet, Daniel R., Centreville, VA, UNITED STATES LaFleur, David W., Washington, DC, UNITED STATES Endress, Gregory A., Potomac, MD, UNITED STATES Ebner, Reinhard, Gaithersburg, MD, UNITED STATES Komatsoulis, George, Silver Spring, MD, UNITED STATES Duan, Roxanne D., Bethesda, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002026040	A1	20020228
	US 6566325	B2	20030520
APPLICATION INFO.:	US 2001-904615	A1	20010716 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-739254, filed on 19 Dec 2000, PENDING Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-97917P	19980825 (60)
	US 1998-98634P	19980831 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS:	23
EXEMPLARY CLAIM:	1
LINE COUNT:	19401

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0264] The translation product of this gene was shown to have homology to the classic MHC transactivator **CIITA** of Mus musculus (See, e.g., Genbank Accession No gil1870520 and AAB48859.1; all references available through this accession are hereby incorporated. . . MHC class II gene expression in B lymphocytes via direct interactation with the MHC class II-specific transcription factors. Furthermore, the **CIITA** protein is thought to play an indirect role in reducing tumorigenicity and inducing long-term tumor immunity.

SUMM [0652] In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or **antisense** DNA or RNA. **Antisense** techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression,CRCPress, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic. . . 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense**--Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as **Antisense**

Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design **antisense** or triple helix polynucleotides in an effort to treat or prevent disease.

SUMM . . . treatingor preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and **antisense** DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires. . .

SUMM . . . into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., **antisense** or **ribozymes**) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can. . .

SUMM [0845] **Antisense** And **Ribozyme** (Antagonists)

SUMM . . . in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, **antisense** sequence is generated internally by the organism, in another embodiment, the **antisense** sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Anitsense Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). **Antisense** technology can be used to control gene expression through **antisense** DNA or RNA, or through triple-helix formation. **Antisense** techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance, Lee et. . .

SUMM [0847] For example, the use of c-myc and c-myb **antisense** RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described.. . . A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given **antisense** RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked. . .

SUMM . . . coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an **antisense** RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The **antisense** RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

SUMM [0849] In one embodiment, the **antisense** nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an **antisense** nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the **antisense** nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired **antisense** RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral,. . .

SUMM [0850] The **antisense** nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a. . . sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded **antisense** nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or **triplex** formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the **antisense** nucleic acid Generally, the larger the hybridizing nucleic acid, the more base

mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or **triplex** as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of. . .

SUMM . . . to either the 5'- or 3'-non-translated, non-coding regions of a polynucleotide sequence of the invention could be used in an **antisense** approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. **Antisense** oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA, **antisense** nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50. . .

SUMM [0853] The **antisense** oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to,. . .

SUMM [0854] The **antisense** oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose,. . .

SUMM [0855] In yet another embodiment, the **antisense** oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a. . .

SUMM [0856] In yet another embodiment, the **antisense** oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the. . .

SUMM [0858] While **antisense** nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region. . .

SUMM [0859] Potential antagonists according to the invention also include catalytic RNA, or a **ribozyme** (See, e.g., PCT International Publication WO 90/11364, published Oct. 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While **ribozymes** that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs corresponding to the polynucleotides of the invention, the use of hammerhead **ribozymes** is preferred. Hammerhead **ribozymes** cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead **ribozymes** is well known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead **ribozyme** cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the **ribozyme** is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the. . .

SUMM [0860] As in the **antisense** approach, the **ribozymes** of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the **ribozyme** may be introduced into the cell in the same manner as described above for the introduction of **antisense** encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the **ribozyme** under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the **ribozyme** to destroy endogenous messages and inhibit translation. Since **ribozymes** unlike **antisense** molecules, are catalytic, a lower intracellular concentration is required for efficiency.

SUMM . . . throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient

(a) an **antisense** molecule directed to the polynucleotide of the present invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention. invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention

DETD . . . that in one orientation, single stranded rescue initiated from the fI ori generates sense strand DNA and in the other, **antisense**.

DETD [1157] In one example, **antisense** technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a. . . of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously **antisense** polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the **antisense** polynucleotide is provided in Example 23.

DETD . . . treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and **antisense** DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the. . .

L3 ANSWER 23 OF 47 USPATFULL

ACCESSION NUMBER:	2002:32691 USPATFULL			
TITLE:	**CIITA**-INTERACTING PROTEINS AND METHODS OF USE THEREFOR			
INVENTOR(S):	GLIMCHER, LAURIE H., WEST NEWTON, MA, UNITED STATES ZHOU, HONG, WILMINGTON, DE, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002019514	A1	20020214	
	US 6410261	B2	20020625	
APPLICATION INFO.:	US 1997-965272	A1	19971106	(8)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **CIITA**-INTERACTING PROTEINS AND METHODS OF USE THEREFOR

AB Isolated nucleic acid molecules encoding a novel protein, CIP104, that interacts with **CIITA**, an MHC class II transcriptional activator, are disclosed. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression. . . methods of modulating CIP104 activity in a cell, and methods for identifying agents that modulate an interaction between CIP104 and **CIITA**.

SUMM [0005] Activation of transcription of the MHC Class II genes has been shown to be dependent upon the transactivator **CIITA** (Steimle et al., 1993, Cell 75:135-146). **CIITA** does not function by directly binding DNA itself but rather by interacting with a conserved set of DNA binding proteins. . . 4:167-178; Mach et al. (1996) Annu. Rev. Immunol. 14:301-331; Riley et al. (1995) Immunity 2:533-543). The transcriptional activation function of **CIITA** has been mapped to an amino terminal acidic domain (amino acids 26-137) (Zhou and Glimcher (1995) Cell 2:545-553). The defect in a subset of MHC Class II deficient patients has been shown to be a mutation in **CIITA**, thereby demonstrating the importance of **CIITA** in regulating MHC Class II gene transcription (Steimle et al., 1993, Cell 75:135-146; Bontron et al. (1997) Hum. Genet. 99:541-546; Steimle et al. (1996) Adv.

Immunol. 61:327-340). Given the critical role that **CIITA** plays in regulating MHC Class II gene expression, further information on how **CIITA** functions is of great interest.

SUMM [0006] This invention pertains to a protein that interacts with **CIITA** and enhances **CIITA**-regulated transciption from MHC class II gene promoters. A nucleic acid molecule encoding a protein that interacts with **CIITA**, termed **CIITA**-interacting protein 104 (also referred to herein as CIP104), has now been isolated and characterized. The CIP104-encoding nucleic acid was isolated based upon the ability of the encoded protein to interact with **CIITA** in a yeast two hybrid assay system. The nucleotide sequence of a cDNA encoding CIP104 and the predicted amino acid. . .

SUMM . . . an amino acid sequence that is homologous to the amino acid sequence of SEQ ID NO: 2 and interacts with **CIITA**. In yet another embodiment, the invention provides an isolated nucleic acid molecule which hybridizes under stringent conditions to a nucleic. . . encoding the amino acid sequence of SEQ ID NO: 2. Isolated nucleic acid molecules encoding CIP104 fusion proteins and isolated **antisense** nucleic acid molecules are also encompassed by the invention.

SUMM [0009] Still another aspect of the invention pertains to isolated **CIITA**-interacting proteins, or portions thereof. In one embodiment, the invention provides an isolated CIP104 protein, or a portion thereof that interacts with **CIITA**. In yet another embodiment, the invention provides an isolated protein which comprises an amino acid sequence homologous to the amino acid sequence of SEQ ID NO: 2 and that interacts with **CIITA**. CIP104 fusion proteins are also encompassed by the invention.

SUMM . . . that modulate the activity or expression of CIP104 and methods for identifying compounds that modulate an interaction between CIP104 and **CIITA**. Screening methods for identifying proteins that interact with CIP are also encompassed by the invention.

DRWD . . . reticulocyte lysate transcription/translation system. pCI.CIP104 (as) represents a control expression vector in which the CIP104-coding sequences are oriented in the **antisense** orientation, which fails to direct expression of a protein. pCI represents the parental control expression vector, which lacks CIP104 coding sequences. pCMV.**CIITA** represents a **CIITA** expression vector, which directs expression of **CIITA** protein.

DRWD . . . of the human MHC class II DR.alpha. promoter, either in the absence (bars 1-4) or in presence (bars 5-8) of **CIITA**.

DRWD . . . of CIP104 on transactivation of the B7.1 promoter, either in the absence (bars 1-4) or in presence (bars 5-8) of **CIITA**.

DETD [0018] This invention pertains to a **CIITA** Interacting Protein 104 (CIP104), a protein that interacts with the MHC class II transcriptional transactivator **CIITA**. A cDNA encoding CIP104 was isolated based upon the interaction of CIP104 with the interaction domain of **CIITA** using a two-hybrid interaction trap assay in yeast (see Example 1). Expression of CIP104 mRNA in various tissue has been. . . expression observed in thymus (see Example 2). Functional studies showed that CIP104 enhances transactivation of MHC class II promoters by **CIITA** (see Example 3).

DETD [0021] As used herein, the term "**CIITA**" is intended to refer to the human MHC Class II transcriptional regulatory protein having the amino acid sequence described in Steimle et al. (1993) Cell 75:135-146, as well as the equivalent protein in other species (e.g., mouse **CIITA**).

DETD [0028] As used herein, an "**antisense**" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, e.g., complementary to. . . a double-stranded cDNA molecule, complementary to an mRNA sequence or complementary to the coding strand of a gene. Accordingly, an **antisense** nucleic acid can hydrogen bond to a sense nucleic acid.

DETD . . . term "biologically active portion of CIP104" is intended to include portions of CIP104 that retain the ability to interact with **CIITA**. The ability of portions of CIP104 to interact with

CIITA can be determined in standard in vitro interaction assays, for example using a **CIITA** fusion protein that comprises the interaction domain of **CIITA** that interacts with CIP104. Nucleic acid fragments encoding biologically active portions of CIP104 can be prepared by isolating a portion. . . . or peptide (e.g., by recombinant expression in a host cell) and assessing the ability of the portion to interact with **CIITA**, for example using a glutathione-S-transferase (GST)-**CIITA** fusion protein.

DETD . . . sequence of SEQ ID NO: 2) without altering the functional activity of CIP104, such as its ability to interact with **CIITA** or its ability to enhance transcription from MHC class II promoters, whereas an "essential" amino acid residue is required for. . .

DETD . . . amino acid sequence at least 60% homologous to the amino acid sequence of SEQ ID NO: 2 and interacts with **CIITA** or enhances transcription from MHC class II promoters. Preferably, the protein encoded by the nucleic acid molecule is at least. . .

DETD . . . at least 60% homologous to the nucleotide sequence of SEQ ID NO: 1 and encodes a protein that interacts with **CIITA** or enhances transcription from MHC class II promoters. Preferably, the nucleotide sequence is at least 70% homologous to SEQ ID. . .

DETD [0052] An isolated nucleic acid molecule encoding a **CIITA** -interacting protein homologous to the protein of SEQ ID NO: 2 can be created by introducing one or more nucleotide substitutions,. . . coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for their ability to interact with **CIITA** (e.g., using a GST-**CIITA** fusion protein) to identify mutants that retain **CIITA**-interacting ability.

DETD . . . mutant protein can be expressed recombinantly in a host cell and the ability of the mutant protein to interact with **CIITA** can be determined using an in vitro interaction assay. For example, a recombinant CIP104 (e.g., a mutated or truncated form of SEQ ID NO: 2) can be radiolabeled and incubated with a GST-**CIITA** fusion protein. Glutathione-sepharose beads are then added to the mixture to precipitate the CIP104-**CIITA**-GST complex, if such a complex is formed. After washing the beads to remove non-specific binding, the amount of radioactive protein. . . amount of radioactive protein remaining in the eluate to thereby determine whether the mutant CIP104 is capable of interacting with **CIITA**.

DETD [0075] Another aspect of the invention pertains to isolated nucleic acid molecules that are **antisense** to the coding strand of a CIP104 mRNA or gene. An **antisense** nucleic acid of the invention can be complementary to an entire CIP104 coding strand, or to only a portion thereof. In one embodiment, an **antisense** nucleic acid molecule is **antisense** to a coding region of the coding strand of a nucleotide sequence encoding CIP104 (e.g., the coding region of SEQ ID NO: 1 comprises nucleotides 509-3343). In another embodiment, the **antisense** nucleic acid molecule is **antisense** to a noncoding region of the coding strand of a nucleotide sequence encoding CIP104. In certain embodiments, an **antisense** nucleic acid of the invention is at least 300, nucleotides in length. More preferably, the **antisense** nucleic acid is at least 400, 500, 600, 700, 800, 900 or 1000 nucleotides in length. In preferred embodiments, an **antisense** of the invention comprises at least 30 contiguous nucleotides of the noncoding strand of SEQ ID NO: 1, more preferably.

DETD [0076] Given the coding strand sequences encoding CIP104 disclosed herein (e.g., SEQ ID NO: 1), **antisense** nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The **antisense** nucleic acid molecule may be complementary to the entire coding region of CIP104 mRNA, or alternatively can be an oligonucleotide which is **antisense** to only a portion of the coding or noncoding region of CIP104 mRNA. For example, the **antisense** oligonucleotide may be complementary to the region surrounding the translation start site of CIP104 mRNA. An **antisense** oligonucleotide can be, for example, about 15, 20, 25,

30, 35, 40, 45 or 50 nucleotides in length. An **antisense** nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an **antisense** nucleic acid (e.g., an **antisense** oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the **antisense** and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the **antisense** nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an **antisense** orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an **antisense** orientation to a target nucleic acid of interest, described further in the following subsection).

DETD [0077] In another embodiment, an **antisense** nucleic acid of the invention is a **ribozyme**. **Ribozymes** are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. A **ribozyme** having specificity for a CIP104-encoding nucleic acid can be designed based upon the nucleotide sequence of a CIP104 cDNA disclosed. . .

DETD . . . further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an **antisense** orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is **antisense** to CIP104 mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the **antisense** orientation can be chosen which direct the continuous expression of the **antisense** RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of **antisense** RNA. The **antisense** expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which **antisense** nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined. . . by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using **antisense** genes see Weintraub, H. et al., **Antisense** RNA as a molecular tool for genetic analysis, Reviews--Trends in Genetics, Vol. 1(1) 1986.

DETD . . . acid sequence at least 60% homologous to the amino acid sequence of SEQ ID NO: 2 and that interacts with **CIITA** or enhances transcription from MHC class II promoters. Preferably, the protein is at least 70% homologous to SEQ ID NO:. . .

DETD . . . portions of the CIP104 protein. For example, the invention further encompasses a portion of a CIP104 protein that interacts with **CIITA**. As demonstrated in the examples, CIP104 protein interacts with the interation domain of **CIITA** (about amino acid positions 134 to 317 of **CIITA**). An in vitro interaction assay (such as that described above in subsection I utilizing a GST-**CIITA** fusion protein comprising the interaction domain of **CIITA**) can be used to determine the ability of CIP104 peptide fragments to interact with the interaction domian of **CIITA** to thereby identify peptide fragments that interact with **CIITA**.

DETD . . . a preferred embodiment, the method identifies compounds that modulate the activity of CIP104 by modulating the interaction between CIP104 and **CIITA**. Accordingly, in a preferred embodiment of the above-described method, the indicator composition comprises a CIP104 protein and a **CIITA** protein and the effect of the test compound on the activity of the CIP104 protein is determined by determining the degree of interaction between the CIP104 protein and the **CIITA** protein the presence and absence of the test compound. The

method can be carried out either in vitro or in vivo in cells. For example, for an in vitro assay, recombinant CIP104 and recombinant **CIITA** can be combined in the presence and absence of a test compound and the degree of interaction between CIP104 and **CIITA** in the presence and absence of the test compound can be determined by standard methods known in the art (e.g., by evaluating the amount of CIP104 co-precipitated with **CIITA** in the presence and absence of the test compound or by labeling one of the two proteins and evaluating the. . . with the nonlabeled protein in the presence and absence of the test compound). For an in vitro assay, CIP104 and **CIITA** can be expressed in a host cell that also contains a reporter gene whose expression is dependent upon interaction of CIP104 and **CIITA**. The effect of a test compound on the interaction between CIP104 and **CIITA** in the cell can then be evaluated by determining the level of expression of the reporter gene in the presence. . . CIP104 (described further in Example 1) can be adapted to identifying test compounds that modulate the interaction of CIP104 with **CIITA**.

DETD . . . preferred embodiment, the method identifies compounds that modulate the activity of CIP104 by modulating the ability of CIP104 to enhance **CIITA**-regulated gene transcription. Accordingly, in another preferred embodiment of the above-described method, the indicator composition is a cell comprising a CIP104 protein, a **CIITA** protein and a reporter gene responsive to **CIITA** and the effect of the test compound on the activity of the CIP104 protein is determined by determining the level. . . expression of the reporter gene in the presence and absence of the test compound. Preferably, the reporter gene responsive to **CIITA** comprises a major histocompatibility complex (MHC) class II gene promoter. A preferred assay system for examining the effect of test compounds on CIP104 enhancement of **CIITA**-regulated gene expression is described further in Example 3, in which a host cell is transfected with (i) an expression vector encoding CIP104, (ii) an expression vector encoding **CIITA** and (ii) a DR.alpha.-CAT reporter gene construct. The level of CAT activity in the host cell in the presence and absence of a test compound can be used to determine the effect of the test compound on CIP104-enhanced **CIITA**-regulated MHC class II gene expression.

DETD [0133] Preferred methods of the invention for identifying agents that modulate the interaction between CIP104 and **CIITA** can comprise, for example,

DETD [0135] (i) CIP104, or an **CIITA**-interacting portion thereof; and

DETD [0136] (ii) an **CIITA**, or a CIP104-interacting portion thereof,

DETD [0139] c) identifying an agent that modulates an interaction between CIP104 and **CIITA**.

DETD [0140] Isolated CIP104 and/or **CIITA** may be used in the method, or, alternatively, only portions of CIP104 and/or **CIITA** may be used. For example, an isolated interaction domain of **CIITA** can be used as the CIP104-interacting portion of **CIITA**. Likewise, a portion of CIP104 capable of binding to the interaction domain of **CIITA** may be used. In a preferred embodiment, one or both of (i) and (ii) are fusion proteins, such as GST. . . non-labeled protein. The assay can be used to identify agents that either stimulate or inhibit the interaction between CIP104 and **CIITA**. An agent that stimulates the interaction between CIP104 and **CIITA** is identified based upon its ability to increase the degree of interaction between (i) and (ii) as compared to the degree of interaction in the absence of the agent, whereas an agent that inhibits the interaction between CIP104 and **CIITA** is identified based upon its ability to decrease the degree of interaction between (i) and (ii) as compared to the. . . domain-ligand interactions as described in U.S. Pat. No. 5,352,660 by Pawson can be adapted to identifying agents that modulate the CIP104/**CIITA** interactions.

DETD . . . An inhibitory agent may function, for example, by directly

inhibiting CIP104 activity or by inhibiting an interaction between CIP104 and **CIITA**. In another embodiment, the agent stimulates CIP104 activity. A stimulatory agent may function, for example, by directly stimulating CIP104 activity or by promoting an interaction between CIP104 and **CIITA**.

DETD . . . encodes the protein or to a second protein with which the first protein normally interacts (e.g., molecules that bind to **CIITA** to thereby inhibit the interaction between CIP104 and **CIITA**). Examples of intracellular binding molecules, described in further detail below, include **antisense** CIP104 nucleic acid molecules (e.g., to inhibit translation of CIP104 mRNA), intracellular anti-CIP104 antibodies (e.g., to inhibit the activity of. . .

DETD [0166] In one embodiment, an inhibitory agent of the invention is an **antisense** nucleic acid molecule that is complementary to a gene encoding CIP104, or to a portion of said gene, or a recombinant expression vector encoding said **antisense** nucleic acid molecule. The use of **antisense** nucleic acids to downregulate the expression of a particular protein in a cell is well known in the art (see e.g., Weintraub, H. et al., **Antisense** RNA as a molecular tool for genetic analysis, Reviews--Trends in Genetics, Vol.1(1)1986; Askari, F. K. and McDonnell, W. M. (1996). . . (1995) Cancer Gene Ther. 2:47-59; Rossi, J. J. (1995) Br. Med. Bull. 51:217-225; Wagner, R. W. (1994) Nature 372:333-335). An **antisense** nucleic acid molecule comprises a nucleotide sequence that is complementary to the coding strand of another nucleic acid molecule (e.g.,. . . an mRNA sequence) and accordingly is capable of hydrogen bonding to the coding strand of the other nucleic acid molecule. **Antisense** sequences complementary to a sequence of an mRNA can be complementary to a sequence found in the coding region of. . . region and an untranslated region (e.g., at the junction of the 5' untranslated region and the coding region). Furthermore, an **antisense** nucleic acid can be complementary in sequence to a regulatory region of the gene encoding the mRNA, for instance a transcription initiation sequence or regulatory element. Preferably, an **antisense** nucleic acid is designed so as to be complementary to a region preceding or spanning the initiation codon on the coding strand or in the 3' untranslated region of an mRNA. An **antisense** nucleic acid for inhibiting the expression of CIP104 protein in a cell can be designed based upon the nucleotide sequence. . .

DETD [0167] An **antisense** nucleic acid can exist in a variety of different forms. For example, the **antisense** nucleic acid can be an oligonucleotide that is complementary to only a portion of a CIP104 gene. An **antisense** oligonucleotides can be constructed using chemical synthesis procedures known in the art. An **antisense** oligonucleotide can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the **antisense** and sense nucleic acids, e.g. phosphorothioate derivatives and acridine substituted nucleotides can be used. To inhibit CIP104 expression in cells in culture, one or more **antisense** oligonucleotides can be added to cells in culture media, typically at about 200 .mu.g oligonucleotide/ml.

DETD [0168] Alternatively, an **antisense** nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an **antisense** orientation (i.e., nucleic acid transcribed from the inserted nucleic acid will be of an **antisense** orientation to a target nucleic acid of interest). Regulatory sequences operatively linked to a nucleic acid cloned in the **antisense** orientation can be chosen which direct the expression of the **antisense** RNA molecule in a cell of interest, for instance promoters and/or enhancers or other regulatory sequences can be chosen which direct constitutive, tissue specific or inducible expression of **antisense** RNA. For example, for inducible expression of **antisense** RNA, an inducible eukaryotic

regulatory system, such as the Tet system (e.g., as described in Gossen, M. and Bujard, H.. . . et al. (1995) Science 268:1766-1769; PCT Publication No. WO 94/29442; and PCT Publication No. WO 96/01313) can be used. The **antisense** expression vector is prepared as described above for recombinant expression vectors, except that the cDNA (or portion thereof) is cloned into the vector in the **antisense** orientation. The **antisense** expression vector can be in the form of, for example, a recombinant plasmid, phagemid or attenuated virus. The **antisense** expression vector is introduced into cells using a standard transfection technique, as described above for recombinant expression vectors.

DETD [0169] In another embodiment, an **antisense** nucleic acid for use as an inhibitory agent is a **ribozyme**. **Ribozymes** are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region (for reviews on **ribozymes** see e.g., Ohkawa, J. et al. (1995) J. Biochem. 118:251-258; Sigurdsson, S. T. and Eckstein, F. (1995) Trends Biotechnol. 13:286-289; Rossi, J. J. (1995) Trends Biotechnol. 13:301-306; Kiehntopf, M. et al. (1995) J. Mol. Med. 73:65-71). A **ribozyme** having specificity for CIP104 mRNA can be designed based upon the nucleotide sequence of the CIP104 cDNA. For example, a. . .

DETD . . . activity of a CIP104 protein are chemical compounds that, directly inhibit CIP104 activity or inhibit the interaction between CIP104 and **CIITA**. Such compounds can be identified using screening assays that select for such compounds, as described in detail above.

DETD . . . inhibitor. A dominant negative inhibitor can be a form of a CIP104 protein that retains the ability to interact with **CIITA** but that lacks one or more other functional activities such that the dominant negative form of CIP104 acts to inhibit the ability of the CIP104/**CIITA** complex to activate transcription. This dominant negative form of a CIP104 protein may be, for example, a mutated form of CIP104 in which the region of the protein that interacts with **CIITA** is conserved but in which one or more amino acid residues elsewhere in the protein are mutated. Such dominant negative. . . cell to allow for expression of the mutated CIP104 protein. The ability of the mutant CIP104 protein to interact with **CIITA** can be assessed using standard in vitro interaction assays. The effect of the mutant CIP104 protein on transcriptional activation can. . . assessing the effect of the mutant CIP104 protein in transcription of the reporter gene. The indicator cells should express endogenous **CIITA** or should be transfected to express **CIITA**. A mutant form of CIP104 that retains the ability to interact with CIP104 but that interferes with transcriptional activation from MHC class II promoters when co-expressed in cells with **CIITA** can be selected as a dominant negative inhibitor of CIP104 activity.

DETD . . . be used to inhibit the activity of a CIP104 protein are chemical compounds that inhibit the interaction between CIP104 and **CIITA**. Such compounds can be identified using screening assays that select for such compounds, as described in detail above.

DETD . . . activity in cells, such as compounds that directly stimulate CIP104 protein and compounds that promote the interaction between CIP104 and **CIITA**. Such compounds can be identified using screening assays that select for such compounds, as described in detail above.

DETD [0181] For stimulatory or inhibitory agents that comprise nucleic acids (including recombinant expression vectors encoding CIP104 protein, **antisense** RNA, intracellular antibodies or dominant negative inhibitors), the agents can be introduced into cells of the subject using methods known. . .

DETD [0189] A modulatory agent, such as a chemical compound that modulates the CIP104/**CIITA** interaction, can be administered to a subject as a pharmaceutical composition. Such compositions typically comprise the modulatory agent and a. . .

DETD . . . defective MHC class II gene expression. In a preferred

embodiment, MHC class II deficiency syndrome caused by a mutation in **CIITA** is treated by providing a normal **CIITA** to the patients (e.g., by gene therapy with a **CIITA** gene) in combination with upregulating CIP104 activity (e.g., by gene therapy with a CIP104 gene).

DETD [0198] A yeast two-hybrid interaction trap assay was used to isolate proteins that could directly bind to the MHC-transactivator protein **CIITA**. A **CIITA**-Gal4 fusion protein was prepared for use as the "bait" in the yeast two-hybrid assay by cloning a fragment of human **CIITA** that had an internal deletion of amino acid residues 21 to 134 (referred to herein as **CIITA**..DELTA.AD) into the vector pEG202 (Gyuris, J. et al. (1993) Cell 75:791-803) to thereby create an in-frame **CIITA**..DELTA.AD-Gal4 fusion. The **CIITA**..DELTA.AD fragment lacks the transcriptional activation domain of **CIITA** (at about residues 21-134) but retains a proline-serine-threonine (P-S-T) rich region at about residues 135-292. This bait was used to. . .

DETD . . . a protein of 945 amino acids having a predicted molecular weight of approximately 104 kD. The encoded protein was termed **CIITA**-Interacting Protein 104 (CIP104). Additional characterization demonstrated that CIP104 was able to interact with a **CIITA** in which the activation domain had been removed (i.e., the **CIITA**..DELTA.AD fragment used to isolate CIP104) but was unable to interact with a fragment of **CIITA** in which both the activation domain and the P-S-T region had been removed. Accordingly, these experiments demonstrate that the P-S-T region of **CIITA** is necessary for binding to CIP104.

DETD . . . protein of the expected molecular weight. In contrast, a control vector in which the CIP104 cDNA was cloned in the **antisense** orientation, pCI.CIP104 (as), did not result in protein production. The parental control vector, pCI, similarly did not direct protein expression. A **CIITA** expression vector, pCMV. **CIITA**, directed expression of a protein of the expected molecular weight.

DETD . . . a DR.alpha. promoter-reporter gene construct (DR.alpha.-CAT) (5 .mu.g) or (ii) both a DR.alpha. promoter-reporter gene construct (5 .mu.g) and a **CIITA** expression vector (1 .mu.g). The total amount of DNA transfected into each cell was brought to 26 .mu.g using control vector DNA. The expression vector in which the CIP104 cDNA was cloned in the **antisense** orientation (PCI.CIP104 (as)) served as a control. The results of these studies are summarized in the graph of FIG. 3, which demonstrates that CIP104 alone (i.e., in the absence of **CIITA**) did not significantly stimulate expression of the DR.alpha.-CAT reporter gene (see bars 1-4 of FIG. 3). In contrast, when CIP104 was coexpressed with **CIITA**, transactivation of the DR.alpha.-CAT reporter gene was upregulated as compared to when **CIITA** was expressed alone (compare lane 5 of FIG. 3 with lanes 6-8). This effect of CIP104 was dose-dependent, with 20 .mu.g of CIP104 stimulating **CIITA**-mediated DR.alpha.-CAT expression approximately 30-fold as compared to **CIITA** alone. No stimulation of **CIITA**-mediated DR.alpha.-CAT expression was observed with the pCI.CIP104 (as) **antisense** control vector. These experiments demonstrate that CIP104 can potentiate the transcriptional activation ability of **CIITA** for MHC class II promoters.

DETD . . . results with the DR.alpha.-CAT reporter gene, no effect on transcription of the B7.1-CAT reporter gene was observed when CIP104 and **CIITA** were coexpressed (see lanes 4-8). Moreover, CIP104 alone did not significantly stimulate B7.1-CAT expression. These results indicate that the synergistic of CIP104 and **CIITA** was not observed with a non-MHC class II promoter.

CLM What is claimed is:

. . . acid sequence at least 60% homologous to the amino acid sequence of SEQ ID NO: 2 and (ii) interacts with **CIITA** or enhances transcription from an MHC class II promoter.

. . . to the nucleotide sequence of SEQ ID NO: 1, wherein the nucleic acid molecule encodes a protein that interacts with **CIITA** or enhances transcription from an MHC class II promoter.

. . . acid sequence at least 60% homologous to the amino acid sequence of SEQ ID NO: 2 and (ii) interacts with **CIITA** or enhances transcription from an MHC class II promoter.

. . . 40. The method of claim 38, wherein the agent is a nucleic acid molecule having a nucleotide sequence that is **antisense** to the coding strand of a CIP104 mRNA or a CIP104 gene.

42. The method of claim 41, wherein: the indicator composition comprises a CIP104 protein and a **CIITA** protein; and the effect of the test compound on the activity of the CIP104 protein is determined by determining the degree of interaction between the CIP104 protein and the **CIITA** protein the presence and absence of the test compound.

43. The method of claim 41, wherein: the indicator composition is a cell comprising a CIP104 protein, a **CIITA** protein and a reporter gene responsive to **CIITA**; and the effect of the test compound on the activity of the CIP104 protein is determined by determining the level. . .
44. The method of claim 43, wherein the reporter gene responsive to **CIITA** comprises a major histocompatibility complex (MHC) class II gene promoter.

L3 ANSWER 24 OF 47 USPATFULL
ACCESSION NUMBER: 2002:346979 USPATFULL
TITLE: Composition for the detection of signaling pathway gene expression
INVENTOR(S): Au-Young, Janice, Berkeley, CA, United States
Seilhamer, Jeffrey J., Los Altos Hills, CA, United States
PATENT ASSIGNEE(S): Incyte Genomics, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6500938	B1	20021231	
APPLICATION INFO.:	US 1998-16434		19980130	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Marschel, Ardin H.
LEGAL REPRESENTATIVE: Incyte Genomics, Inc.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 6180
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . polynucleotide probes can be DNA or RNA, or any RNA-like or DNA-like material. The polynucleotide probes can be sense or **antisense** polynucleotide probes. Where target polynucleotides are double stranded, the probes may be either sense or **antisense** strands. Where the target polynucleotides are single stranded, the nucleotide probes are complementary single strands.
DETD . . . alpha subunit. [human.]
SEQ ID NO: 802 515253 1228944 protein tyrosine phosphatase epsilon M. [Norway rat.]
SEQ ID NO: 803 515399 414113 (**MHC**) **class II transactivator**. [human.]
SEQ ID NO: 804 515847 1902984 lectin-like oxidized LDL receptor. [human.]

SEQ ID NO: 805 516219 1245048 serine/threonine kinase. [Caenorhabditis elegans.]
SEQ. . .
DETD . . . derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171). **Antisense** RNA (aRNA) was generated using T7 RNA polymerase following the first round of cDNA synthesis. aRNA was then random-primed to. . .

L3 ANSWER 25 OF 47 USPATFULL
ACCESSION NUMBER: 2002:311029 USPATFULL
TITLE: METHOD OF MODULATING THE EFFICIENCY OF TRANSLATION TERMINATION AND DEGRADATION OF ABERRANT MRNA INVOLVING A SURVEILLANCE COMPLEX COMPRISING HUMAN UPF1P, EUCARYOTIC RELEASE FACTOR 1 AND EUCARYOTIC RELEASE FACTOR 3
INVENTOR(S): Peltz, Stuart, 67 Castle Pointe Blvd., Piscataway, NJ, United States 08854
Czaplinski, Kevin, 115 Hollywood Ave., Somerset, NJ, United States 08873
Weng, Youmin, 2 Indian Spring Rd., Cranford, NJ, United States 07016

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6486305	B1	20021126
APPLICATION INFO.:	US 2000-639987		20000816 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-86260, filed on 28 May 1998, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: McCarry, Sean
ASSISTANT EXAMINER: Zara, Jane
LEGAL REPRESENTATIVE: Lyon & Lyon LLP
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 2808
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . a) providing a cell containing a vector comprising the nucleic acid encoding proteins of the complex, the complex; or an **antisense** molecule thereof; b) overexpressing said nucleic acid in said cell to produce an overexpressed complex so as to interfere with. . .
DETD . . . inhibit the decay pathway, stabilize nonsense transcripts or modulate the efficiency of translation termination are important for the success of **antisense** RNA technology. **Antisense** RNAs are small, diffusible, untranslated and highly structured transcripts that pair to specific target RNAs at regions of complementarity, thereby controlling target RNA function or expression. However, attempts to apply **antisense** RNA technology have met with limited success. The limiting factor appears to be in achieving sufficient concentrations of the **antisense** RNA in a cell to inhibit or reduce the expression of the target gene. It is likely that one impediment to achieving sufficient concentration is the nonsense decay pathway, since the short **antisense** RNA transcripts, which are not meant to encode a gene product, will likely lead to rapid translation termination if translation occurs, and consequently to rapid degradation and low abundance of the **antisense** RNA in the cell. Thus, the agents of the invention that stabilize aberrant mRNA transcripts may also stabilize **antisense** RNAs.
DETD This approach utilizes **antisense** nucleic acid and **ribozymes** to block translation of a specific mRNA, either by masking that mRNA with an **antisense** nucleic acid or cleaving it with a **ribozyme**.

DETD **Antisense** nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule. . . to that mRNA, forming a double stranded molecule. The cell does not translate an mRNA in this double-stranded form. Therefore, **antisense** nucleic acids interfere with the expression of mRNA into protein. Oligomers of about fifteen nucleotides and molecules that hybridize to. . . are easy to synthesize and are likely to pose fewer problems than larger molecules when introducing them into organ cells. **Antisense** methods have been used to inhibit the expression of many genes in vitro (Marcus-Sekura, 1988, supra; Hambor et al., 1988,. . .

DETD **Ribozymes** are RNA molecules possessing the ability to specifically cleave other single stranded RNA molecules in a manner somewhat analogous to DNA restriction endonucleases. **Ribozymes** were discovered from the observation that certain mRNAs have the ability to excise their own introns. By modifying the nucleotide. . .

DETD Investigators have identified two types of **ribozymes**, Tetrahymena-type and "hammerhead"-type. Tetrahymena-type **ribozymes** recognize four-base sequences, while "hammerhead"-type recognize eleven- to eighteen-base sequences. The longer the recognition sequence, the more likely it is to occur exclusively in the target mRNA species. Therefore, hammerhead-type **ribozymes** are preferable to Tetrahymena-type **ribozymes** for inactivating a specific mRNA species, and eighteen base recognition sequences are preferable to shorter recognition sequences.

DETD . . . cell, said method comprising: a) providing a cell containing a vector comprising the nucleic acid encoding the complex; or an **antisense** thereof; b) overexpressing said nucleic acid vector in said cell to produce an overexpressed complex so as to interfere or. . .

DETD . . . POTASSIUM CHANNEL, INWARDLY-RECTIFYING, SUBFAMILY J, MEMBER 1, PLAKOPHILIN 1, PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE ISOFORM 1B, ALPHA SUBUNIT, PLECTIN 1, SHORT STATURE, **MHC CLASS II TRANSACTIVATOR**, HYPOPHOSPHATEMIA, VITAMIN D-RESISTANT RICKETS, RIEG BICOID-RELATED HOMEOBOX TRANSCRIPTION FACTOR 1, MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2E, RETINITIS PIGMENTOSA-3, MutS, E. COLI,. . .

DETD . . . and/or degradation of aberrant transcripts in a cell in a cell, said method comprising: a) providing a cell; b) expressing **antisense** transcript of the complex in sufficient amount to bind to the complex.

DETD In one embodiment, a nucleic acid encoding the complex or factors of the complex; an **antisense** or **ribozyme** specific for the complex, or specific for regions of the release factors and Upf1p, are introduced in vivo in a. . .

DETD . . . invention provides for co-expression of a gene product that modulates activity at the peptidyl transferase center and a therapeutic heterologous **antisense** or **ribozyme** gene under control of the specific DNA recognition sequence by providing a gene therapy expression vector comprising both a gene. . . peptidyl transferase center (including but not limited to a gene for a mutant frameshift or mRNA decay protein, or an **antisense** RNA or **ribozyme** specific for mRNA encoding such a protein) with a gene for an unrelated **antisense** nucleic acid or **ribozyme** under coordinated expression control. In one embodiment, these elements are provided on separate vectors; alternatively these elements may be provided. . .

L3 ANSWER 26 OF 47 USPATFULL

ACCESSION NUMBER:	2002:238872 USPATFULL
TITLE:	Design principle for construction of expression constructs for gene therapy
INVENTOR(S):	Wittig, Burghardt, Berlin, GERMANY, FEDERAL REPUBLIC OF Junghans, Claas, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S):	Soft Gene GmbH, Berlin, GERMANY, FEDERAL REPUBLIC OF

(non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6451593	B1	20020917
APPLICATION INFO.:	US 1999-310842		19990512 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 1997-DE2704, filed on 13 Nov 1997		

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1996-19648625	19961113

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Priebe, Scott D.
ASSISTANT EXAMINER: Kaushal, Sumesh
LEGAL REPRESENTATIVE: Nils H. Ljungman & Associates
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1703
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . peptides, cytokines, or components of the regulation of the cell cycle, or for the synthesis of regulative RNA molecules and **antisense** RNA, **ribozyme** or mRNA-editing-RNA. Furthermore, an important aspect of the invention is that the construction principle allows for the covalent linking of. . .

SUMM . . . non-tumor cells, such as antigen-presenting cells (macrophages, dendritic cells). Alternatively, genes which control the expression of peptide-presenting proteins, such as **CIITA** or ICSBP are of great importance.

SUMM . . . the uptake of these complexes into the cytosol after endosomal uptake (Plank et.al., J.Biol.Chem.269, 12918, (1994)). The covalent attachment of **antisense** desoxyoligonucleotides to haemagglutinine peptide is described by Bongartz et al. (Nuc.Acids Res. 22, 4681, 1994).

SUMM . . . peptides, cytokines, or components of the regulation of the cell cycle, or for the synthesis of regulative RNA-molecules, such as **antisense**-RNA, **ribozymes** or mRNA-editing RNA. Since the nucleic acid is covalently closed on both ends and no free hydroxyl-groups are available for. . .

SUMM . . . or components of the regulation of the cell cycle, or for the synthesis of regulative RNA molecules and anti-sense RNA, **ribozyme** or mRNA-editing RNA.

SUMM . . . of advantage for the transcription of genes coding for RNA. Such promoter sequences can result in the expression of short **antisense**-RNAs, **ribozymes**, and artificial mRNA in vivo. RNA-polymerase III produces significantly more copies of RNA than polymerase II and has an exact. . .

SUMM . . . CD40, B7-1, and B7-2, proteins of the MHC-complexes I or II or .beta.-2 microglobulin, interferone consensus sequence binding protein ICSBP, **CIITA**, Flt3, or entire proteins or fragments thereof of presentable epitopes from tumor specific expressed mutated or non-mutated proteins, e.g. Ki-RAS-fragments,. . .

DETD . . . employing said process"; U.S. Pat. No. 5,624,803 entitled "In vivo oligonucleotide generator, and methods of testing the binding affinity of **triplex** forming oligonucleotides derived therefrom"; U.S. Pat. No. 5,889,169 entitled "Cell cycle regulatory protein p16 gene"; U.S. Pat. No. 5,858,679 entitled. . . cells in a genomically heterogeneous cellular sample"; U.S. Pat. No. 5,652,222 entitled "Selective inhibition of leukemic cell proliferation by bcr-abl **antisense** oligonucleotides"; U.S. Pat. No. 5,369,008 entitled "Methods for the detection of BCR-ABL and abnormal ABL proteins in leukemia patients"; U.S.. . . U.S. Pat. No. 5,677,165 entitled "Anti-CD40 monoclonal antibodies capable of blocking B-cell activation";

U.S. Pat. No. 5,877,021 entitled "B7-1 targeted **ribozymes**"; U.S. Pat. No. 5,747,034 entitled "Methods and materials for the induction of T cell anergy"; U.S. Pat. No. 5,738,852 entitled. . . targeted delivery of drugs"; U.S. Pat. No. 5,883,223 entitled "CD9 antigen peptides and antibodies thereto"; U.S. Pat. No. 5,877,022 entitled "**Ribozymes** targeted to APO(a) RNA"; U.S. Pat. No. 5,874,250 entitled "DNA encoding for a protein containing the extracellular domain of lymphocyte. . .

DETD . . . brain and therapeutic uses therefor"; U.S. Pat. No. 5,602,240, entitled "Backbone modified oligonucleotide analogs"; U.S. Pat. No. 5,631,359, entitled "Hairpin **ribozymes**"; and U.S. Pat. No. 5,610,289, entitled "Backbone modified oligonucleotide analogues"; which are incorporated by reference, as if set forth in. . .

L3 ANSWER 27 OF 47 USPATFULL

ACCESSION NUMBER:	2002:95541 USPATFULL
TITLE:	Method for screening compounds capable of inhibiting binding between the transcription factor of STAT1 and the transcription factor of USF1
INVENTOR(S):	Mach, Bernard, Chambesy, SWITZERLAND
PATENT ASSIGNEE(S):	Novimaune S.A., SWITZERLAND (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6379894	B1	20020430
APPLICATION INFO.:	US 2000-641999		20000818 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 1999-FR376, filed on 19 Feb 1999		

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1998-2025	19980219

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Horlick, Kenneth R.
LEGAL REPRESENTATIVE:	Lerner, David, Littenberg, Krumholz & Mentlik, LLP
NUMBER OF CLAIMS:	15
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	965

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . a method for identifying compounds capable of inhibiting activation by cytokines, in particular by interferon .gamma., of expression of the **CIITA** gene which itself is involved in controlling and regulating the expression of genes coding for MHC class II molecules.

SUMM The Applicant has previously identified and characterized one of these factors, the **CIITA** factor (class II transactivator) [STEIMLE et al., 1993, Cell 75, 135-146 and EP-A-0 648 836]. Further, International patent application WO-A-9606107 has shown that there are two domains in the **CIITA** factor which are more involved in activation of transcription of MHC class II genes. However, surprisingly and in contrast to. . . II genes [COGSWELL et al., 1991, Crit. Rev. Immunol. 11, 87-112], STEIMLE et al have shown that expression of the **CIITA** factor coincides closely with expression of MHC class II genes and is absolutely required both for constitutive expression and for. . . extinction of MHC class II genes during differentiation of plasmocytes is associated with extinction of the gene coding for the **CIITA** factor.

SUMM Further, LENNON et al (1997, Immunogenetics, 45, 266-273) have identified the promoter sequence of a **CIITA** gene which is responsible for differential expression of this factor in B cells. However, the existence of this single sequence does not explain why differential expression of the **CIITA** factor is observed in different cell types. Further, it does not account for induction by

cytokines.

SUMM . . . samples from different tissues of human origin to identify the complex organisation of sequences providing control of expression of the **CIITA** factor, the Applicant isolated and characterized several promoter regions and the Applicant demonstrated the existence of different forms of the **CIITA** factor and also different **CIITA** genes. These studies have formed the basis of a publication (MUHLETHALER-MOTTET et al., 1997, EMBO J., 16, 2851-2860) and form. . . that the different promoters identified can be activated selectively: two of the promoters are responsible for constitutive expression of the **CIITA** gene in dendritic cells (promoter I) and in B lymphocytes (promoter III) while promoter IV is involved in expressing the **CIITA** gene after induction by a cytokine, in particular interferon .gamma..

SUMM The implication of such a JAK/STAT1 activation system in the control of expression of **CIITA** genes inducible by interferon .gamma. has been the subject of studies which have established that, as with other genes which are inducible by interferon .gamma., expression of the **CIITA** factor cannot be induced in cell lines which are deficient for JAK1 (CHANG et al., 1994, J. Exp. Med., 180,. . .

SUMM Similarly, MERAZ et al. (1996, Cell, 84, 431-442) have shown that **CIITA** gene expression is not induced by interferon Y in bone marrow macrophages from the STAT1.sup.-/.sup.- mouse, suggesting a determining role for STAT1 in inducing the expression of the **CIITA** gene by interferon .gamma..

SUMM Further, LEE and BENVENISTE (1996, J. Immunol. 157, 1559-1568) have carried out experiments using **antisense** oligonucleotides specific for the nucleic acid sequence coding for the STAT1 protein factor to demonstrate that the reduction in the expression of the STAT1 protein is accompanied by a reduction in the expression of the **CIITA** gene which can be observed after induction by interferon .gamma..

SUMM . . . sequence known as the "GAS element" (DARNELL, 1997, Science 277, 1630-1635). An analysis of the promoter IV sequence of the **CIITA** gene (inducible by cytokines: MUHLETHALER-MOTTET et al., 1997, EMBO J. 16, 2851-2860--and FIG. 1) has revealed the presence of such. . .

SUMM . . . the activity of the STAT1 factor. The discovery of this mechanism, in particular involved in activating the expression of the **CIITA** gene by interferon .gamma., and as a result in inducing MHC class II molecules by interferon .gamma., has led the. . . particularly under the control of all or a portion of promoter IV. Preferably, said gene is the gene coding for **CIITA**.

SUMM The term "nucleic acid sequence coding for the **CIITA** polypeptide" means the sequence in question comprises all or a portion of a nucleic acid sequence corresponding to mRNA from different tissues or cell lines expressing a **CIITA** activity in a constitutive manner or after induction. Thus they can be at least partially coding sequences or, for example,. . .

DETD . . . .beta. lactamase gene, or 2) code for all or a portion of polypeptides with the amino acid sequence of a **CIITA** factor as described in French patent application 97 04954, and more particularly as defined by SEQ ID NO: 2 (as. . . Table 2). In the latter case, it can be said that they code for all or a portion of the **CIITA** polypeptide.

DETD . . . nucleic acid sequence coding for all or a portion of a polypeptide, preferably for all or a portion of the **CIITA** polypeptide (SEQ ID NO: 2) or for all or a portion of a reporter gene placed under the control of. . .

DETD . . . nucleic acid sequence coding for all or a portion of a polypeptide, preferably for all or a portion of the **CIITA** polypeptide (SEQ ID NO:2) or for all or a portion of a reporter gene, the expression of which is placed. . .

DETD . . . acid sequence coding for all or a portion of a polypeptide, in particular for all or a portion of the **CIITA** polypeptide or

for all or a portion of a reporter gene placed under the control of all or a portion. . .

DETD . . . acid sequence coding for all or a portion of a polypeptide, in particular for all or a portion of the **CIITA** polypeptide (SEQ ID NO: 2) or for all or a portion of a reporter gene, placed under the control of. . .

DETD . . . acid sequence coding for all or a portion of a polypeptide, in particular for all or a portion of the **CIITA** polypeptide (SEQ ID NO: 2) or for all or a portion of a reporter gene, placed under the control of. . .

DETD . . . acid sequence coding for all or a portion of a polypeptide, in particular for all or a portion of the **CIITA** polypeptide (SEQ ID NO: 2) or for all or a portion of a reporter gene, placed under the control of. . .

DETD . . . 16, 2851-2860). The plasmid PIV-308 comprises the -308 to +75 fragment of the region flanking the promoter IV of the **CIITA** gene sub cloned downstream of the gene coding for the rabbit beta globulin of the pG.beta.G(+) plasmid. The activity of. . .

DETD . . . gel electrophoresis to obtain labelled double strand DNA probes corresponding to all or a portion of the promoter IV of **CIITA**.

DETD In order to evaluate directly the role of STAT1 in regulating the expression of the **CIITA** gene after activation by interferon .gamma., the induction capacity of the **CIITA** gene was studied in a cell line which was deficient for STAT1 (U3A) and in a cell line expressing STAT1. . .

DETD In contrast to that observed for the 2FTGH line, in the U3A line, expression of **CIITA** messenger RNA or activation of the **CIITA** promoter IV were not induced by the cytokine, as shown by RNAse protection experiments and analysis of the promoter function. . .

DETD The results showed that STAT1 controls the activation of the **CIITA** promoter IV by interferon .gamma.. These results agree with the work of MERAZ et al., 1996, Cell, 84, 431-442 which shows that **CIITA** messenger RNA cannot be induced by interferon .gamma. in macrophages from STAT-/-mice.

DETD In order to analyse the role of STAT1 in **CIITA** promoter IV and its presence in the U complex, said protein complex, associated with the labelled NGE probe, was analysed. . .

DETD . . . major role played by the E-box during induction by interferon .gamma.. The nucleic acid sequence of the E-box of the **CIITA** promoter IV has the consensus sequence CACGTG previously described as a helix/loop/helix/leucine zipper protein DNA binding site.

DETD . . . in U and L protein complexes. In order to confirm that the USF1 factor is capable of binding to the **CIITA** promoter IV, EMSA experiments were carried out in the presence of USF1 recombinant proteins. The results showed that the USF1 protein is effectively present in the U and L complexes and specifically binds to the **CIITA** promoter IV.

CLM What is claimed is:

5. A method according to claim 3, wherein said polypeptide is the **CIITA** polypeptide (SEQ ID NO:2).

. . . 9. A method according to claim 8, wherein said nucleic acid sequence codes for all or a portion of the **CIITA** polypeptide (SEQ ID NO:2).

L3 ANSWER 28 OF 47 USPATFULL

ACCESSION NUMBER: 2002:70008 USPATFULL

TITLE: Methimazole derivatives and tautomeric cyclic thiones to treat autoimmune diseases

INVENTOR(S): Kohn, Leonard D., Bethesda, MD, United States
Curley, Robert W., Columbus, OH, United States
Rice, John M., West Chester, OH, United States

PATENT ASSIGNEE(S): Sentron Medical, Inc., Rockville, MD, United States

(U.S. corporation)
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6365616	B1	20020402
APPLICATION INFO.:	US 1999-382960		19990825 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-141311, filed on 31 Aug 1998, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Criares, Theofore J.
LEGAL REPRESENTATIVE: Frost Brown Todd LLC
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 17 Drawing Page(s)
LINE COUNT: 3028
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . 75: 871-878 (1992); Montani et al., Endocrinology. 139: 290-302 (1998)). Finally, it has been shown that MMI decreases expression of **CIITA** increased class II expression and this appears to be related to the action of MMI to enhance Y box protein. . .

SUMM . . . and in inhibiting IFN-induced Class II RNA expression than methimazole; (b) inhibit the action of IFN by acting on the **CIITA**/Y-box regulatory system; (c) may be significantly more soluble than methimazole, leading to significant formulation flexibility and advantages; (d) have less. . .

DETD Two factors known to regulate class II gene expression in immune cells are the class II transactivator (**CIITA**) and a Y box binding protein (Ting J P-Y, et al., ibid (1993); Reith W, et al., ibid (1995)). **CIITA** is a non DNA-binding protein transactivator that functions as a molecular switch to control constitutive and inducible MHC class II gene expression in immune cells; **CIITA** expression is induced by .gamma.-IFN and is believed to be involved in its activity (Steimle V, et al., Science 265:106-109. . . cells (Ting J P-Y, et al., J. Exp. Med. 179:1605-1611 (1994); MacDonald G H, et al., J. Biol.Chem. 270:3527-3533 (1995)). **CIITA** can induce the formation of the complex induced by .gamma.-IFN and associated with aberrant class II gene expression in FRTL-5. . .

DETD . . . the interferon-induced class I activity requires the presence of the CRE; this is consistent with recent results indicating that interferon-induced **CIITA** is the mediator of the increase in class I as well as class II activity and requires the CRE for. . .

DETD . . . which was derived from interferon-treated rat FRTL-5 cell RNA using a sense primer having the nucleotide sequence, 5'-AGCAAGCCAGTCACAGAAGG-3', and an **antisense** primer with the sequence, 5'-GATTCGACTTGGAAGATGCC-3', two regions which are highly conserved in the class II nucleotide and protein sequence. After. . .

DETD . . . that .gamma.-IFN simultaneously reduces class II suppressive action by decreasing TSEP-1 RNA levels and increases class II expression by increasing **CIITA** RNA levels. The net result is "aberrant" expression of MHC class II and abnormal class I expression. Methimazole reverses this. . .

L3 ANSWER 29 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:423722 BIOSIS
DOCUMENT NUMBER: PREV200200423722
TITLE: **CIITA**-interacting proteins and methods of use therefor.
AUTHOR(S): Glimcher, Laurie H.; Zhou, Hong Yan (1)
CORPORATE SOURCE: (1) Wilmington, DE USA
ASSIGNEE: President and Fellows of Harvard College
PATENT INFORMATION: US 6410261 June 25, 2002

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 25, 2002) Vol. 1259, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

TI **CIITA**-interacting proteins and methods of use therefor.

AB Isolated nucleic acid molecules encoding a novel protein, CIP104, that interacts with **CIITA**, an MHC class II transcriptional activator, are disclosed. The invention further provides **antisense** nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression. . . methods of modulating CIP104 activity in a cell, and methods for identifying agents that modulate an interaction between CIP104 and **CIITA**.

IT Major Concepts
Clinical Chemistry (Allied Medical Sciences)

IT Chemicals & Biochemicals
CIITA-interacting proteins

L3 ANSWER 30 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:928873 CAPLUS
DOCUMENT NUMBER: 138:299406
TITLE: The phage .lambda. CII transcriptional activator carries a C-terminal domain signaling for rapid proteolysis
AUTHOR(S): Kobiler, Oren; Koby, Simi; Teff, Dinah; Court, Donald; Oppenheim, Amos B.
CORPORATE SOURCE: Department of Molecular Genetics and Biotechnology, Hebrew University-Hadassah Medical School, Jerusalem, 91120, Israel
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(23), 14964-14969
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB ATP-dependent proteases, like FtsH (HflB), recognize specific protein substrates. One of these is the .lambda. CII protein, which plays a key role in the phage lysis-lysogeny decision. Here we provide evidence that the conserved C-terminal end of CII acts as a necessary and sufficient cis-acting target for rapid proteolysis. Deletions of this conserved tag, or a mutation that confers two aspartic residues at its C terminus do not affect the structure or activity of CII. However, the mutations abrogate CII degrdn. by FtsH. We have established an in vitro assay for the .lambda. CIII protein and demonstrated that CIII directly inhibits proteolysis by FtsH to protect CII and CII mutants from degrdn. Phage .lambda. carrying mutations in the C terminus of CII show increased frequency of lysogenization, which indicates that this segment of CII may itself be sensitive to regulation that affects the lysis-lysogeny development. In addn., the region coding for the C-terminal end of CII overlaps with a gene that encodes a small **antisense** RNA called OOP. We show that deletion of the end of the cII gene can prevent OOP RNA, supplied in trans, interfering with CII activity. These findings provide an example of a gene that carries a region that modulates stability at the level of mRNA and protein.

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CIITA** (class II transactivator); phage .lambda. CII transcriptional activator carries C-terminal domain for proteolysis)

IT **Antisense** RNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(OOP RNA of phage .lambda., mediating CII mRNA degrdn.; phage .lambda. CII transcriptional activator carries C-terminal domain for proteolysis)

L3 ANSWER 31 OF 47 USPATFULL

ACCESSION NUMBER:	2001:155766 USPATFULL
TITLE:	49 human secreted proteins
INVENTOR(S):	Moore, Paul A., Germantown, MD, United States Ruben, Steven M., Oley, MD, United States Olsen, Henrik S., Gaithersburg, MD, United States Shi, Yanggu, Gaithersburg, MD, United States Rosen, Craig A., Laytonsville, MD, United States Florence, Kimberly A., Rockville, MD, United States Soppet, Daniel R., Centreville, VA, United States Lafleur, David W., Washington, DC, United States Endress, Gregory A., Potomac, MD, United States Ebner, Reinhard, Gaithersburg, MD, United States Komatsoulis, George, Silver Spring, MD, United States Duan, Roxanne D., Bethesda, MD, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001021700	A1	20010913
APPLICATION INFO.:	US 2000-739254	A1	20001219 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-97917P	19980825 (60)
	US 1998-98634P	19980831 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS:	23
EXEMPLARY CLAIM:	1
LINE COUNT:	15462

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0225] The translation product of this gene was shown to have homology to the classII MHC transactivator **CIITA** of Mus musculus (See, e.g., Genbank Accession No gil1870520 and AAB48859.1; all references available through this accession are hereby incorporated. . . MHC class II gene expression in B lymphocytes via direct interactation with the MHC class II-specific transcription factors. Furthermore, the **CIITA** protein is thought to play an indirect role in reducing tumorigenicity and inducing long-term tumor immunity.

SUMM [0594] In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or **antisense** DNA or RNA. **Antisense** techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression,CRCPress, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic. . . 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (**antisense**-Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while **antisense** RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design **antisense** or triple helix polynucleotides in an effort to treat or prevent disease.

SUMM . . . or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and **antisense** DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires. . .

SUMM . . . into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., **antisense** or **ribozymes**) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can. . .

SUMM [0787] **Antisense** And **Ribozyme** (Antagonists)

SUMM . . . in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, **antisense** sequence is generated internally by the organism, in another embodiment, the **antisense** sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Anitsense Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). **Antisense** technology can be used to control gene expression through **antisense** DNA or RNA, or through triple-helix formation. **Antisense** techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). Triple helix formation is discussed in, for instance, Lee et. . .

SUMM [0789] For example, the use of c-myc and c-myb **antisense** RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described.. . . A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given **antisense** RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked. . .

SUMM . . . coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an **antisense** RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The **antisense** RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

SUMM [0791] In one embodiment, the **antisense** nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an **antisense** nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the **antisense** nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired **antisense** RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral,. . .

SUMM [0792] The **antisense** nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a. . . sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded **antisense** nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or **triplex** formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the **antisense** nucleic acid Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or **triplex** as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of. . .

SUMM . . . 5' - or 3' - non-translated, non-coding regions of a polynucleotide sequence of the invention could be used in an **antisense** approach to inhibit translation of endogenous mRNA.

Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. **Antisense** oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5' -, 3' - or coding region of mRNA, **antisense** nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50. . .

SUMM [0795] The **antisense** oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to,. . .

SUMM [0796] The **antisense** oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose,. . .

SUMM [0797] In yet another embodiment, the **antisense** oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a. . .

SUMM [0798] In yet another embodiment, the **antisense** oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the. . .

SUMM [0800] While **antisense** nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region. . .

SUMM [0801] Potential antagonists according to the invention also include catalytic RNA, or a **ribozyme** (See, e.g., PCT International Publication WO 90/11364, published Oct. 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While **ribozymes** that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs corresponding to the polynucleotides of the invention, the use of hammerhead **ribozymes** is preferred. Hammerhead **ribozymes** cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement. . . is that the target mRNA have the following sequence of two bases: 5' -UG-3'. The construction and production of hammerhead **ribozymes** is well known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead **ribozyme** cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the **ribozyme** is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the. . .

SUMM [0802] As in the **antisense** approach, the **ribozymes** of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the **ribozyme** may be introduced into the cell in the same manner as described above for the introduction of **antisense** encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the **ribozyme** under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the **ribozyme** to destroy endogenous messages and inhibit translation. Since **ribozymes** unlike **antisense** molecules, are catalytic, a lower intracellular concentration is required for efficiency.

SUMM . . . throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an **antisense** molecule directed to the polynucleotide of the present invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention. invention, and/or (b) a **ribozyme** directed to the polynucleotide of the present invention

DETD . . . that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, **antisense**.

DETD [1065] In one example, **antisense** technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a. . . of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously **antisense** polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the **antisense** polynucleotide is provided in Example 23.

DETD . . . treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and **antisense** DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the. . .

L3 ANSWER 32 OF 47 USPATFULL

ACCESSION NUMBER:	2001:235085 USPATFULL
TITLE:	Gene expression profiles in normal and cancer cells
INVENTOR(S):	Vogelstein, Bert, Baltimore, MD, United States Kinzler, Kenneth W., BelAir, MD, United States Zhang, Lin, Baltimore, MD, United States Zhou, Wei, Baltimore, MD, United States
PATENT ASSIGNEE(S):	The JohnsHopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6333152	B1	20011225	
APPLICATION INFO.:	US 1998-81646		19980520	(9)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Fredman, Jeffrey			
LEGAL REPRESENTATIVE:	Bannee & Witcoff			
NUMBER OF CLAIMS:	19			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	6 Drawing Figure(s); 2 Drawing Page(s)			
LINE COUNT:	2244			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The present invention further includes **antisense** oligonucleotides complementary in whole or in part to SEQ ID NOS: 1-734.

DETD . . . to the sequences shown in, SEQ ID NOS:1-870, or their complements, this invention also provides the anti-sense polynucleotide stand, e.g. **antisense** RNA to these sequences or their complements. One can obtain an **antisense** RNA using the sequences provided in SEQ ID NOS:1-734 and the methodology described in Vander Krol et al. (1988) Bio. . .

DETD . . . B).

S73483 phosphorylase kinase catalytic subunit PHKG2 homol

11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301 H. sapiens mRNA for **MHC class II transactivator**.

U28687 Human zinc finger containing protein ZNF157 (ZNF 15

U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG

U56236 Human Fc. . .

DETD . . . B).

S73483 phosphorylase kinase catalytic subunit PHKG2 homol

11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301 H. sapiens mRNA for **MHC class II transactivator**.

U28687 Human zinc finger containing protein ZNF157 (ZNF 15

U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG
U56236 Human Fc. . .
DETD . . . B).
S73483 phosphorylase kinase catalytic subunit PHKG2 homol
11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301
H. sapiens mRNA for **MHC class II transactivator.**
U28687 Human zinc finger containing protein ZNF157 (ZNF 15
U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG
U56236 Human Fc. . .
DETD . . . B).
S73483 phosphorylase kinase catalytic subunit PHKG2 homol
11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301
H. sapiens mRNA for **MHC class II transactivator.**
U28687 Human zinc finger containing protein ZNF157 (ZNF 15
U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG
U56236 Human Fc. . .
DETD . . . B).
S73483 phosphorylase kinase catalytic subunit PHKG2 homol
11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301
H. sapiens mRNA for **MHC class II transactivator.**
U28687 Human zinc finger containing protein ZNF157 (ZNF 15
U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG
U56236 Human Fc. . .
DETD . . . B).
S73483 phosphorylase kinase catalytic subunit PHKG2 homol
11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301
H. sapiens mRNA for **MHC class II transactivator.**
U28687 Human zinc finger containing protein ZNF157 (ZNF 15
U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG
U56236 Human Fc. . .
DETD . . . B).
S73483 phosphorylase kinase catalytic subunit PHKG2 homol
11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301
H. sapiens mRNA for **MHC class II transactivator.**
U28687 Human zinc finger containing protein ZNF157 (ZNF 15
U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG
U56236 Human Fc. . .
DETD . . . B).
S73483 phosphorylase kinase catalytic subunit PHKG2 homol
11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301
H. sapiens mRNA for **MHC class II transactivator.**
U28687 Human zinc finger containing protein ZNF157

(ZNF 15
U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG
U56236 Human Fc. . .
DETD . . . B).
S73483 phosphorylase kinase catalytic subunit PHKG2 homol
11 CATGTTGGCCAGGCT H1025322 124 194 63 111 51 X74301
H. sapiens mRNA for **MHC class II transactivator**.
U28687 Human zinc finger containing protein ZNF157 (ZNF 15
U29119 Human leiomyoma LM-196.4 ectopic sequence from HMG
U56236 Human Fc. . .

L3 ANSWER 33 OF 47 USPATFULL
ACCESSION NUMBER: 2001:231143 USPATFULL
TITLE: Arrays for identifying agents which mimic or inhibit the activity of interferons
INVENTOR(S): Silverman, Robert H., Beachwood, OH, United States
Williams, Bryan R. G., Cleveland, OH, United States
Der, Sandy, Cleveland, OH, United States
PATENT ASSIGNEE(S): The Cleveland Clinic Foundation, Cleveland, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6331396	B1	20011218
APPLICATION INFO.:	US 1999-405438		19990923 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-101497P	19980923 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Zitomer, Stephanie
ASSISTANT EXAMINER: Forman, B J
LEGAL REPRESENTATIVE: Calfee, Halter & Griswold LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 9639
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM Alternatively, the ISG in a culture of human cells is suppressed by transfecting the cells with **antisense** cDNA, or **antisense** oligonucleotide, or PNA, or a dominant negative mutant ISG. Cells in which the ISG expression is inhibited or suppressed are. . .
DETD . . . for non-histone chro 2008 -98 NC 0 0
20 NC
0 0 -700 D 1.5 0.37
X74301 H. sapiens mRNA for **MHC class II transactivator** -- Also Represents: U18259 -1 * 4 NC
0 0 -4 NC 0 0 52 I .about.2.6 0.37
X86691 H. sapiens. . .

L3 ANSWER 34 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:277727 CAPLUS
DOCUMENT NUMBER: 132:318607
TITLE: Sequences of a novel transcription factor of MHC class II genes, substances capable of inhibiting this new transcription factor, and medical uses of said substances
INVENTOR(S): Masternak, Krzysztof; Reith, Walter; Mach, Bernard
PATENT ASSIGNEE(S): Novimmune S.A., Switz.

SOURCE: Eur. Pat. Appl., 48 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 995798	A1	20000426	EP 1998-120085	19981024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2000024766	A2	20000504	WO 1999-EP8026	19991022
WO 2000024766	A3	20000817		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1124953	A2	20010822	EP 1999-970995	19991022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002156258	A1	20021024	US 2001-840243	20010424

PRIORITY APPLN. INFO.: EP 1998-120085 A 19981024
WO 1999-EP8026 W 19991022

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The invention provides sequences of a novel transcription factor of MHC class II genes, inhibitors of this transcription factor capable of down-regulating the expression of MHC class II mols., and medical uses of these inhibitors. The novel transcription factor, called RFX-ANK, is a 33 kDa subunit of the RFX transcription complex, possesses a series of ankyrin repeats and a well defined protein-protein interaction motif, and is essential for binding the RFX complex to the conserved X box motif of MHC II promoters. The gene encoding RFX-ANK, which was mapped to 19p12, is capable of fully correcting the MHC II expression deficiency found in cell lines from patients having an autosomal recessive disease resulting from mutations in the regulatory genes responsible for the expression of MHC II genes. The invention further provides inhibitors of RFX-ANK, including antibodies, RFX-ANK mutants/derivs./fragments, **ribozymes**, and **antisense** mols. The inhibitors of the invention are also useful as immunosuppressants for the treatment and prevention of diseases assocd. with aberrant expression of MHC class II genes.

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CIITA**, member of RFX transcription complex; sequences of a subunit (RFX-ANK) of the RFX transcription complex, substances capable of inhibiting this new transcription factor, and medical uses of said substances)

IT **Antisense** oligonucleotides
Ribozymes
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use as RFX-ANK inhibitor; sequences of a novel transcription factor of MHC class II genes, substances capable of inhibiting this new transcription factor, and medical uses of said substances)

L3 ANSWER 35 OF 47 USPATFULL
ACCESSION NUMBER: 2000:105716 USPATFULL
TITLE: Methods of disrupting interferon signal transduction

pathways
INVENTOR(S): Sedmak, Daniel, Columbus, OH, United States
Miller, Daniel, Hilliard, OH, United States
Rahill, Brian, Columbus, OH, United States
Zhang, Yingxue, Columbus, OH, United States
PATENT ASSIGNEE(S): Ohio State Research Foundation, Columbus, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6103531		20000815	
APPLICATION INFO.:	US 1999-249154		19990212	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-74575P	19980213	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schwartzman, Robert A.
ASSISTANT EXAMINER: Ousley, Andrea
LEGAL REPRESENTATIVE: Calfee, Halter & Griswold LLP
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 370
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . enhance the expression of specific genes. For example, IFN-.gamma. requires a functional JAK/STAT pathway to upregulate the class II transactivator, **CIITA**, and thereby induce MHC class II expression.
SUMM . . . present method is useful for blocking the activation of interferon stimulated genes such as for example, the gene that encodes **CIITA**. The present method is also a useful research tool for characterizing the JAK1 pathway. As such, the present method is. . .
SUMM . . . CMV DNA polymerase activity such as, for example, phosphonoformic acid (PFA,) and ganciclovir (GCV). Alternatively, the cells are treated with **antisense** oligodeoxynucleotides (ODN) to the CMV DNA polymerase prior to infection. The ODN function by binding to sense mRNA molecules and. . . translation, it is preferred that the 5' region of the mRNA overlapping the AUG initiation codon be used as an **antisense** target. Preferably, each ODN is synthesized on a DNA synthesizer using phosphoramidite chmistry and derivitized to the phosphorothioates using the. . . . .mu.M ODN in the presence of cationic liposomes. Quantitative Western blot analysis is used to assess the efficacy of the **antisense** oligonucleotides in preventing CMV DNA polymerase expression.

L3 ANSWER 36 OF 47 USPATFULL
ACCESSION NUMBER: 2000:40875 USPATFULL
TITLE: Human LIG-1 homolog (HLIG-1)
INVENTOR(S): Wu, Shujian, Levittown, PA, United States
Sweet, Raymond W, Bala Cynwyd, PA, United States
Truneh, Alemseged, West Chester, PA, United States
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6046030		20000404	
APPLICATION INFO.:	US 1997-986485		19971208	(8)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1997-59448P	19970922	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted

PRIMARY EXAMINER: Caputa, Anthony C.
ASSISTANT EXAMINER: Gucker, Stephen
LEGAL REPRESENTATIVE: Han, William T.Ratner & Prestia, King, William T.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 2648
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . protein "18 wheeler," the neural development protein slit, the receptors for chorionic gonadotropin, lutrophin, and follitrophin, and the transcriptional regulator, **CIITA**. The crystal structure of one member of this family, porcine ribonuclease inhibitor (RI), has been determined (B. Kobe and J.. . .

SUMM . . . of the gene encoding endogenous HLIG-1 can be inhibited using expression blocking techniques. Known such techniques involve the use of **antisense** sequences, either internally generated or separately administered. See, for example, O'Connor, J Neurochem (1991) 56:560 in Oligodeoxynucleotides as **Antisense** Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988). Alternatively, oligonucleotides which form triple helices with the gene can. . .

DETD . . . the cDNA from human cDNA libraries using sequential rounds of nested PCR with two sets of primers. One set of **antisense** primers is specific to the 5' end of the partial cDNA and the other set of primers anneals to a. . .

DETD . . . artifactual, probably occurring during CHOT1 cloning, since it lies in the extreme 5' untranslated segment of CHOT1 and matches the **antisense** strand of human and mouse LIG-1 within the protein coding region.

L3 ANSWER 37 OF 47 USPATFULL
ACCESSION NUMBER: 2000:15639 USPATFULL
TITLE: Regulation of gene expression
INVENTOR(S): Peyman, John A., Cheshire, CT, United States
PATENT ASSIGNEE(S): Yale University, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6022863		20000208	
APPLICATION INFO.:	US 1996-646789		19960521	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Martinell, James
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 77
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 43 Drawing Figure(s); 28 Drawing Page(s)
LINE COUNT: 4750
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . class II gene expression by IFN-.gamma. is initiated by Jak-STAT activation, but also requires the de novo production of the **CIITA** factor (Steimle et al., 1993, Cell 75:135-146; Steimle et al., 1994, Science 265:106-109; Chang et al., 1994, J. Exp. Med.. . .

SUMM . . . antigens, receptors, transporters, and other intracellular proteins (Simonsen and Lodish, 1994, Trends in Pharmacol. Sci. 15:437-441). The cDNA encoding the **CIITA** transcription factor was cloned by functional complementation of the recessive MHC class II.sup.- -phenotype in a cell line derived from. . .

DRWD FIGS. 8A and B. STAT1 localization in HeLa cells expressing sense and **antisense** TSU RNA. Batches of stable transfectants were prepared as in FIGS. 7A-C, treated with IFN-.gamma. for 2 days, fixed with. . .

DRWD . . . blot analysis of expression of TSU RNA in placenta, and reactivation of STAT1 function by treatment of trophoblasts with TSU **antisense** oligonucleotide. Poly-A.sup.+ RNA (2 .mu.g) from 16 normal human tissues was analyzed by probing Northern blots with a .sup.32 P-labeled TSU **antisense** RNA probe, as described infra

Section 7.1.6. Autoradiographic exposure shown was produced by exposure with an intensifying screen for 8. . .

DETD In a specific embodiment, the oligonucleotide comprises catalytic RNA, or a **ribozyme** (see, e.g., PCT International Publication WO 90/11364, published Oct. 4, 1990; Sarver et al., 1990, Science 247:1222-1225). In another embodiment,. . .

DETD . . . fusion partners for negative controls because no specific suppression is known to occur in these cells. The class II transactivator, **CIITA**, which is constitutively expressed in B lymphocyte lines (Steimle et al., 1993, Cell 75:135-146) is known to directly stimulate MHC. . . lines (Steimle et al., 1994, Science 265:106-109; Chang et al., 1994, J. Exp. Med. 180:1367-74). The regulation of expression of **CIITA** in trophoblasts has not been characterized, and the suppression observed in these experiments may involve one or more steps in. . .

DETD . . . and the conserved AA with AC. The predicted folding of these synthetic oligonucleotides is shown in FIG. 10. The TSU **antisense** and sense phosphorothioate oligonucleotides were based on a sequence between motifs 6 and 7. The following phosphorothioate oligodeoxynucleotides were synthesized,. . .

DETD . . . isolated from 16 normal human tissues and displayed on formaldehyde-agarose gels, and Northern blots were prepared (Clontech). .sup.32 P-labeled TSU **antisense** RNA probe was synthesized by in vitro transcription using Not I-linearized TSU-pCR3 reversed construct and T7 RNA polymerase as described. . .

DETD . . . mouse IgG.sub.2, produced faint background staining with punctate nucleolar signals under all conditions. The HeLa-TSU-pCR3-reversed orientation transfectant cells (producing TSU **antisense** RNA) (FIG. 7B) responded to IFN-.gamma. by inducing expression of HLA-DR antigen and increasing the constitutive expression of HLA-A, B,. . . TSU probe indicated that copy numbers of integrated plasmids were similar, and Northern blot analysis of recombinant TSU sense and **antisense** RNA from these stable transfectant batches showed similar production of recombinant mRNA (data not shown). The cytomegalovirus promoter drives high-level,. . .

DETD . . . Biol. 14:2170-2179). To determine whether the function of STAT1 was impaired in TSU-transfectants, batches of cells expressing either sense or **antisense** TSU RNA were treated with IFN-.gamma. for 2 days and STAT1 was localized with a specific mAb (See Materials and. .

DETD . . . stably transfected HeLa cells were reduced to background levels by the sense TSU RNA gene product, but not by the **antisense** RNA gene product. In addition, STAT1 function was blocked by the transfected TSU sense RNA gene product, not by the **antisense** RNA gene product. These results are consistent with the idea that the effect of the TSU cDNA in transfected cell. . .

DETD . . . goat TSU-related EST had no common open reading frames, but showed conservation of IFN-signal transduction target motifs. 2) Sense and **antisense** TSU cDNA expression constructs demonstrated qualitatively different suppression of MHC antigen expression and of STAT1 function in transfected cells. 3). . .

L3 ANSWER 38 OF 47 USPATFULL

ACCESSION NUMBER: 2000:15517 USPATFULL

TITLE: Regulatory genetic DNA that regulates the Class II transactivator (**CIITA**)

INVENTOR(S): Ting, Jenny Pan-Yun, Chapel Hill, NC, United States
Piskurich, Janet, Chapel Hill, NC, United States

PATENT ASSIGNEE(S): University of North Carolina at Chapel Hill, Chapel Hill, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6022741		20000208	
APPLICATION INFO.:	US 1997-816617		19970313	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: McKelvey, Terry
LEGAL REPRESENTATIVE: Myers Bigel Sibley & Sajovec, P.A.
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 1420
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Regulatory genetic DNA that regulates the Class II transactivator (**CIITA**)

AB Novel DNAs that regulate expression of the Class II Transactivator (**CIITA**) gene are disclosed. Recombinant DNA comprising **CIITA** regulatory elements operably associated with a heterologous DNA are also disclosed. Additionally, assay systems for identifying compounds that regulate expression. . .

SUMM The present invention relates to DNA regulatory elements that control expression of the Class II Transactivator (**CIITA**) gene. In addition, the present invention discloses assay systems for identifying compounds that alter major histocompatability (MHC) antigen gene expression.

SUMM . . . gene expression occurs at the transcriptional level. Figueiredo et al., J. Immunol. 143, 3781-3786 (1989). Expression of the recently identified **MHC class II transactivator**, **CIITA**, closely parallels class II MHC antigen gene expression. Steimle et al., Cell 75, 135-46 (1993). It has also been shown that **CIITA** is induced by IFN-.gamma., and transfection of **CIITA** alone into cells is sufficient to activate class II MHC, li, and DM genes. See, e.g., Chin et al., Immunity 1, 679 (1994); Chang et al., J. Exper. Med. 180, 1367-1374 (1994); Steimle et al., Science 265, 106-08 (1994). **CIITA** transcript is expressed constitutively in class II MHC-positive cells; however, it can be induced in certain cell types such as. . . glioblastoma cells upon treatment with IFN-.gamma.. See Chang et al., supra; Steimle et al. (1994), supra, 106-08. The kinetics of **CIITA** induction by IFN-.gamma. precedes the induction of class II MHC transcripts, and introduction of **CIITA** alone into a number of cell types is sufficient to activate class II MHC antigen genes.

SUMM The N-terminus of the **CIITA** protein contains an acidic domain (amino acids 30-160), followed by domains rich in proline (amino acids 163-195), serine (amino acids. . . . However, it is likely that the acidic domain alone is not sufficient to activate the class II MHC promoter in **CIITA**, and that the acidic domains of other transcription factors behave differently from the **CIITA** acidic domain. Zhou et al., Immunity 2, 545-553 (1995). Analysis of the primary amino acid sequence of **CIITA** does not show any homology to known conserved DNA-binding motif of transcription factors, and in vitro translated **CIITA** apparently does not interact with DNA. Steimle et al. (1993), supra.

SUMM **CIITA** is now recognized as a "master control" molecule that transactivates all class II MHC genes, as well as genes necessary for the function of class II MHC molecules. In total, **CIITA** regulates at least seventeen genes, all of which are involved in immune activation. Because **CIITA** plays a central role in inducing expression of the class II MHC genes and orchestrating helper T cell activation, **CIITA** is implicated in the etiology of AIDs, transplant rejection, and autoimmune disease states (e.g., lupus, arthritis, diabetes, and multiple sclerosis).. . .

SUMM . . . present invention discloses the identification of novel DNAs, which control the expression of a master molecule, the Class II transactivator (**CIITA**). **CIITA** regulates at least seventeen genes, all involved in immune activation. The DNAs provided by the present investigations can be used to identify compounds that modulate **CIITA** expression, and thereby alter class II

MHC-associated molecules and functions.

DRWD FIG. 1. Map of the genomic DNA contained in the twelve isolated human **CIITA** clones showing the relative location of each clone. DNA was digested with Hind III and analyzed by Southern blotting. The. . . Clones 10 and 12 (grey boxes) were chosen for additional Southern blot analyses localizing the 5'-flanking region of the human **CIITA** gene.

DRWD FIGS. 2A-C. Localization of the 5' UTR, exon 1, and the transcription start site of the **CIITA** gene in the genomic **CIITA** clone 10.

DRWD FIG. 2A. Map of the human genomic **CIITA** clone 10. The 5' UTR oligonucleotide hybridizes to an Xba I fragment of approximately 6.7 kb. The location of the. . .

DRWD . . . I-Xba I fragment (see FIG. 2B--nucleotides 5720 to 6678 of SEQ ID NO:1) surrounding the first exon of the human **CIITA** gene. Exon I sequences are underlined. The 3' end of exon 1 of the human **CIITA** gene was determined by a comparison of the genomic DNA sequence to the sequence of the human **CIITA** cDNA (Steimle et al. Cell 75, 135-46 (1993)), and the 5' end of exon 1 was determined by mapping the. . . the primer extension was the reverse complement of the sequences designated underlined by an arrow. The end of the human **CIITA** cDNA that has been reported by Steimle et al. is marked by an arrowhead. The start site of transcription is. . .

DRWD FIG. 3. Schematic diagram of the **CIITA** regulatory element constructs. A Tfi I DNA fragment (nucleotides 5122 to 6374 of SEQ ID NO:1--see FIG. 2B) containing 112. . . bp of 5' UTR (shown as a small black box) and 1124 bp of 5' flanking sequences of the human **CIITA** gene were cloned upstream of the luciferase reporter gene (vertical lined box) in the pGL2-Basic vector (Promega) to create the. . . I fragment. This central fragment was added to p-2158CIITA.Luc reconstituting in the plasmid p6374CIITA.Luc the approximately 6.4 kb of native **CIITA** 5' flanking sequences (including the 5' end of the **CIITA** gene), excluding the 304 bp Tfi I-Xba I fragment (nucleotides 6374 to 6678 of SEQ ID NO:1) found at the. . .

DRWD FIG. 4. Activity of the **CIITA** regulatory element in a human B cell line. Transient transfections of Raji cells using 10 .mu.g of plasmid DNA were. . .

DRWD FIG. 5. Activity of the **CIITA** regulatory element in an IFN-.gamma. responsive glioblastoma cell line. U373 MG cells were transiently transfected by electroporation using 10 .mu.g. . .

DRWD FIG. 6. TGF-.beta.1 suppresses IFN-.gamma.-induction of the regulatory sequences of the **CIITA** gene in RAW 264.7 cells. RAW 264.7 cells were transiently transfected with the p-2158CIITA.Luc plasmid using DEAE-dextran. Cells were plated. . .

DRWD FIGS. 7A-B. STAT1 regulates induction of the 5' flanking region of the human **CIITA** gene by IFN-.gamma.. The data presented in panels A and B are from different experiments.

DETD The isolated DNAs of the present invention encode regulatory elements for the Class II Transactivator (**CIITA**) gene. A DNA "regulatory element" as used herein is any DNA sequence that regulates gene expression at the transcriptional level (i.e., activates and/or suppresses). A "Class II Transactivator regulatory element" (**CIITA** regulatory element) is a DNA sequence that regulates transcription of the **CIITA** gene. The **CIITA** regulatory elements disclosed herein that activate transcription of the **CIITA** gene, increase **CIITA** gene transcription by at least 50%, more preferably by at least 100%, 150%, 200%, or even 300%, or more. **CIITA** regulatory elements disclosed herein that suppress **CIITA** gene transcription do so by at least 25%, more preferably by at least 35%, 50%, 60%, 75%, or even 85%,. . .

DETD The **CIITA** regulatory elements of the present invention are located within the approximately 6.4 kb of flanking DNA of the **CIITA** gene (nucleotides 1 to 6374 of the 6678 bp Xba I fragment of SEQ ID NO:1). This approximately 6.4 kb. . . DNA fragment is primarily comprised of flanking genomic DNA, but it also includes 112 bp

of 5' UTR of the **CIITA** gene (see FIGS. 2A-C). It will be apparent that other sequence fragments from the human **CIITA** 5' flanking region, longer or shorter than the foregoing sequence, or with minor additions, deletions, or substitutions made thereto, can be prepared which will also carry the **CIITA** regulatory element, all of which are included within the present invention.

DETD The isolated DNAs comprising the **CIITA** regulatory elements can be from any species of origin, including mouse, rat, rabbit, cat, porcine, and human, but are preferably of mammalian origin. In one preferred embodiment of the invention, the isolated DNA encoding the **CIITA** regulatory element has the sequence given as SEQ ID NO:1. In other preferred embodiments, the sequence of the isolated DNA encoding the **CIITA** regulatory element corresponds to a continuous segment of DNA within the DNA given as SEQ ID NO:1, including but not. . . to 3562 of SEQ ID NO:1, and the continuous segment given as nucleotides 1 to 2182 of SEQ ID NO:1. **CIITA** regulatory elements of the present invention include DNA molecules that regulate expression of the **CIITA** gene and have sequences that are substantially homologous to the DNA sequences comprising the **CIITA** regulatory elements disclosed herein, and particularly the human **CIITA** regulatory element disclosed herein as SEQ ID NO:1. **CIITA** regulatory elements of the present invention also encompass DNA molecules that regulate expression of the **CIITA** gene and have sequences that are substantially homologous to continuous segments of DNA located within SEQ ID NO:1, including but. . . 2182 of SEQ ID NO:1. This definition is intended to include natural allelic variations in the DNA sequence comprising the **CIITA** regulatory element. As used herein, regions that are "substantially homologous" are at least 75%, and more preferably are 80%, 85%,. . .

DETD **CIITA** regulatory elements from other species include those which are at least about 75 percent homologous (and more preferably 80%, 85%, 90% or even 95% homologous) to the human **CIITA** regulatory elements disclosed herein, in particular the **CIITA** regulatory element having the sequence given herein as SEQ ID NO:1 and which are capable of regulating the transcription of the **CIITA** gene. **CIITA** regulatory elements from other species also include those which are at least about 75 percent homologous (and more preferably 80%, 85%, 90% or even 95% homologous) to a continuous segment of the **CIITA** regulatory elements as defined herein as SEQ ID NO:1, and which are capable of regulating the transcription of the **CIITA** gene, including but not limited to the continuous segment given herein as nucleotides 1 to 3562 of SEQ ID NO:1,. . .

DETD . . . hybridization assay. (See SAMBROOK ET AL., MOLECULAR CLONING, A LABORATORY MANUAL (2d ed. 1989)). In general, DNA sequences which comprise **CIITA** regulatory elements and which hybridize to the DNA comprising the **CIITA** regulatory elements disclosed herein will be at least 75%, 80%, 85%, 90% or even 95% homologous or more with the DNA sequences of the **CIITA** regulatory elements disclosed herein.

DETD Knowledge of the nucleotide sequence of the **CIITA** regulatory elements disclosed herein can be used to generate hybridization probes which specifically bind to the 5' flanking genomic DNA of the **CIITA** gene to determine the presence of this region of genomic DNA, by Southern hybridization for example. Probes also serve as primers for use in amplifying the **CIITA** gene, or portions thereof, by polymerase chain reaction (PCR) in accordance with the process described in U.S. Pat. Nos. 4,683,202. . .

DETD The **CIITA** regulatory elements provided by the present invention interact with transcription factors to regulate transcription of the **CIITA** gene. Regulation of transcription refers to altering or modulating (i.e., activating or suppressing) the level of transcription. The DNA regulatory. . . so as to effect changes in gene transcription. Alternatively, the transcription factor, regulatory factor, or intracellular signalling molecule may alter **CIITA** gene transcription by interacting with DNA binding proteins that are

bound to the **CIITA** regulatory element and only secondarily with the **CIITA** regulatory element itself.

DETD In one preferred embodiment of the invention, the isolated **CIITA** regulatory element comprises an interferon-.gamma. (IFN-.gamma.) responsive regulatory element, such that the **CIITA** regulatory element modulates (i.e., activates or suppresses) transcription of the **CIITA** gene in response to cellular stimulation by IFN-.gamma.. In another preferred embodiment, the isolated DNA comprises a transforming growth factor-.beta.. . . . element, a glutamate responsive regulatory element, a cAMP agonist responsive regulatory element, or a granulocyte-macrophage-CSF responsive regulatory element. Alternatively, the **CIITA** regulatory elements are responsive to steroid hormones, protein hormones, growth factors, neurotransmitters, and cytokines (including monokines and lymphokines).

DETD The present invention also provides recombinant DNAs comprising a **CIITA** regulatory element operably associated with heterologous DNA. The **CIITA** regulatory element is operably associated with the heterologous DNA such that the **CIITA** regulatory element is functionally linked to the heterologous DNA, and can thereby alter transcription of the heterologous DNA. Typically, the **CIITA** regulatory element will be located 5' to the heterologous DNA, but it may also be located 3' to the heterologous. . . . as it is operably associated therewith. There are no particular upper or lower limits as to the distance between the **CIITA** regulatory element and the heterologous DNA, as long as the two DNA segments are operably associated with each other.

DETD Alternatively, the heterologous DNA can be used to express **antisense** RNAs. In general, "**antisense**" refers to the use of small, synthetic oligonucleotides to inhibit gene expression by inhibiting the function of the target mRNA. . . . coding (sense) sequences in a specific mRNA target by hydrogen bonding according to Watson-Crick base pairing rules. The mechanism of **antisense** inhibition is that the exogenously applied oligonucleotides decrease the mRNA and protein levels of the target gene. Milligan, J. F.. . . . (1993). See also Helene, C. and Toulme, J., Biochim. Biophys. Acta 1049, 99-125 (1990); Cohen, J. S., Ed., OLIGODEOXYNUCLEOTIDES AS **ANTISENSE** INHIBITORS OF GENE EXPRESSION, CRC Press:Boca Raton, Fla. (1987).

DETD A vector is a replicable DNA construct. Vectors are used herein to amplify DNA encoding the **CIITA** regulatory elements as given herein or recombinant DNA as given herein. Alternately, vectors are used herein to express DNA comprising. . .

DETD . . . inducible promoter. For example, as described hereinbelow, it is often desirable to use inducible promoters to identify compounds that stimulate **CIITA** gene expression. One can also use inducible promoters to identify compounds that suppress the induction of gene expression by another compound. As a further alternate, it is sometimes advantageous to use constitutive promoters to identify compounds that suppress **CIITA** gene expression.

DETD Transformed host cells are cells which have been transformed or transfected with vectors containing DNA comprising **CIITA** regulatory elements or recombinant DNA as given hereinabove. Transformed host cells ordinarily express protein, but host cells transformed for purposes. . .

DETD The invention disclosed herein provides cells containing recombinant DNA encoding a **CIITA** regulatory element operably associated with a heterologous DNA, as described hereinabove. Cells of the present invention can be of prokaryotic,. . .

DETD . . . one can transform mammalian cells by the method of co-transformation with a selectable marker and a recombinant DNA encoding a **CIITA** regulatory element operably associated with a heterologous DNA, as described hereinabove. An example of a suitable selectable marker is dihydrofolate. . .

DETD The **CIITA** protein is essential for the expression of fourteen different genes that code for class II transplantation molecules as well

as. . .

DETD Accordingly, the **CIITA** regulatory elements disclosed herein find use as the basis of a rapid screening assay for compounds that regulate the expression of **CIITA**, and hence all class II MHC antigen expression. The present investigations have identified **CIITA** regulatory elements that modulate transcription of the **CIITA** gene in response to IFN-.gamma. and TGF-.beta.. Other compounds can be screened for those that regulate **CIITA** gene transcription through the **CIITA** regulatory elements disclosed herein. The screening assay comprises contacting a test compound to a cell containing a recombinant DNA encoding a **CIITA** regulatory element operably associated with a heterologous DNA, and then detecting a change in the transcription of said heterologous DNA.. . . A change in transcription of the heterologous DNA is an indicator that the test compound regulates (i.e., activates or suppresses) **CIITA** gene transcription. Activating compounds according to this embodiment of the invention will activate **CIITA** gene transcription by at least 50%, more preferably by at least 100%, 150%, 200%, or even 300%, or more. Suppressing compounds according to this embodiment of the invention will suppress **CIITA** gene transcription by at least 25%, more preferably by at least 35%, 50%, 60%, 75%, or even 85%, or more.

DETD . . . IL-1, IL-4, dexamethasone (or other glucocorticoid), glutamate, a cAMP agonist, or granulocyte-macrophage-CSF. A compound can control the activity of the **CIITA** regulatory elements disclosed herein either directly or indirectly, as described in more detail hereinbelow.

DETD Some cell types exhibit constitutive expression of the **CIITA** gene (i.e., the **CIITA** gene is always expressed), whereas in other cell types expression of **CIITA** is inducible (i.e., the **CIITA** gene is not normally expressed, but is induced or "turned on" in response to an external factor). Examples of cell types that constitutively express **CIITA** include B lymphocytes, lymphoma cells, and dendritic cells. In contrast, astrocytes, macrophages, monocytes, glioblastoma cell lines, endothelial cells, Langerhans cells, fibroblasts and microglia cells show inducible expression of **CIITA**. In one embodiment of the invention, cells that exhibit inducible expression of **CIITA** are used to identify compounds that activate or enhance **CIITA** gene transcription (e.g., IFN-.gamma.). In another embodiment, cells that show inducible expression of **CIITA** are used to identify compounds that suppress the induction of **CIITA** gene expression by another compound (e.g., TGF-.beta. suppresses IFN-.gamma. induced **CIITA** gene expression). In a further alternate embodiment of the invention, cells that exhibit constitutive expression of **CIITA** are used to identify compounds that suppress **CIITA** gene transcription.

DETD Recombinant DNA encoding the **CIITA** regulatory element operably associated with heterologous DNA can be constructed by any suitable technique known in the art. A test. . .

DETD The screening assay identifies test compounds that activate or suppress the **CIITA** regulatory element so as to activate or suppress transcription of the heterologous DNA. Compounds that alter transcription of the heterologous DNA are characterized as exhibiting "class II MHC regulatory activity." Compounds that activate **CIITA** gene transcription will activate by at least 50%, more preferably by at least 100%, 150%, 200%, or even 300%, or more. Compounds that suppress **CIITA** gene transcription will suppress by at least 25%, more preferably by at least 35%, 50%, 60%, 75%, or even 85%,. . . underlying the screening assay is that the expression of class II MHC genes is regulated at the transcriptional level, and **CIITA** regulates the transcription of all class II MHC genes. Thus, compounds identified as controlling **CIITA** gene expression by the screening assay disclosed herein are excellent candidates for molecules that regulate the entire complement of class. . .

DETD . . . invention, it is envisioned that some class II MHC regulatory

compounds will not interact directly with the DNA comprising the **CIITA** regulatory element. Instead, these compounds may trigger the synthesis or activation of intracellular signalling molecules or transcription factors that will interact directly with the **CIITA** regulatory element or with other compounds bound thereto as described hereinabove (i.e., such a model has been proposed for the intracellular actions of protein hormones). Alternatively, some class II MHC regulatory compounds will interact directly with the **CIITA** regulatory element or other compounds bound thereto as described hereinabove (i.e., such a model has been proposed for the intracellular. . .

DETD This screening assay is advantageous because **CIITA** expression is reflective of the expression of all genes known to exist in the class II MHC pathway as well as functional genes necessary for the execution of this pathway. Using the **CIITA** regulatory element in a screening assay, large numbers of compounds can be rapidly tested for activity in regulating class II. . .

DETD Isolation and Characterization of Human **CIITA** Genomic Clones

DETD To isolate genomic clones containing the 5'-flanking region of the human **CIITA** gene, approximately one million recombinants from a commercially prepared .lambda.FIX II human fibroblast genomic library (Catalog #946204, Stratagene, La Jolla,. . . 3'--SEQ ID NO:2) and the reverse compliment of nt 375 to 395 (5' CCTCCCTGGTCTCTTCATCAC 3'--SEQ ID NO:3) of the human **CIITA** cDNA sequence as reported by Steimle et al. (Cell 75, 135-46 (1993)). A human **CIITA** cDNA (Riley et al., Immunity 2, 533-43 (1995)) (generously provided by Dr. Jeremy M. Boss) was used as a template. . .

DETD Twelve overlapping **CIITA** genomic clones were isolated, plaque purified, and mapped by Southern blot analyses (FIG. 1). DNA prepared from each clone by. . . 5' AGGATGCCTTCGGATGCCCAGCTCAGAAGC 3' (SEQ ID NO:4), which corresponds to the reverse complement of nt 15 to 44 of the human **CIITA** cDNA sequence described above (also see FIG. 2C), was 5'-end-labeled using T4 polynucleotide kinase (New England Biolaboratories) and .gamma.-[.sup.32 P]-ATP. . .

DETD . . . 5463-67 (1977)), using Sequenase (United States Biochemical Corp., Cleveland, Ohio) (FIG. 2C). The 3' end of exon 1 of human **CIITA** was determined by a comparison of the genomic DNA sequence to the sequence of the human **CIITA** cDNA (Steimle et al., Cell 75, 135-46 (1993)), and the 5' end of exon 1 was determined by mapping the. . .

DETD Identification of **CIITA** Transcriptional Start Site by Primer Extension

DETD Primer extension analysis of the **CIITA** mRNA was performed using Raji poly A+RNA as previously described (Wright et al., J. Exp. Med. 181, 1459-71 (1995)) using. . . above. Absolute product lengths were obtained by comparison to a sequencing ladder. One predominant transcriptional start site for the human **CIITA** gene was identified (FIG. 2C). This start site is located very close (within 4 bp) to the end of the human **CIITA** cDNA reported by Steimle et al. (Cell 75, 135-46 (1993)).

DETD . . . of SEQ ID NO:1), containing 112 bp of 5' UTR and 1124 bp of 5' flanking sequences of the human **CIITA** gene (FIGS. 2B and 2C). This Tfi I fragment was blunted and cloned into the Sma I site upstream of. . . 3562 to 5720 of SEQ ID NO:1) was added to p-2158CIITA.Luc reconstituting in plasmid, p6374CIITA.Luc, the native 6374 bp of **CIITA** 5' flanking sequences (including the 5' end of the **CIITA** gene) found in the original Xba I fragment, excluding the 304 bp Tfi I-Xba I fragment (nucleotides 6374 to 6678. . .

DETD Activity of the **CIITA** Regulator Element in a Human B Cell Line

DETD Raji cells, which exhibit constitutive expression of the **CIITA** gene, were transiently transfected with the human genomic CITA constructs as described in Example 6. Forty-eight hours after transfection, cells. . . transfection with pGL2-Basic. It appears that the p657CIITA. Luc and p1236CIITA.Luc constructs contain regulatory sequences driving constitutive expression of the **CIITA** gene in

Raji cells.

DETD Activity of the **CIITA** Regulatory Element in an IFN-.gamma. Responsive Glioblastoma Cell Line

DETD U373 MG cells, which express MHC class II antigens in response to IFN-.gamma., were transiently transfected with the human genomic **CIITA** constructs as described in Example 6. Transfected cells were treated with 500 U/ml of recombinant human IFN-.gamma. for 16 hours. . .

DETD To further localize the IFN-.gamma. responsive element within the 5' flanking sequences of the **CIITA** gene, U373 MG cells were transiently transfected with the p-2158CIITA and p-3538CIITA.Luc constructs and the fold induction in luciferase activity. . .

DETD TGF-.beta.1 Suppresses Inducibility of the 5' Flanking Region of the **CIITA** Gene in Response to IFN-.gamma.

DETD . . . Recent data indicate that pretreatment of macrophage cell lines with TGF-.beta.1 causes a reduction in the increased levels of steady-state **CIITA** mRNA that occur in response to IFN-.gamma.. Nandan & Reiner, J. Immunol. 158, 1095-1101 (1997); Lee et al., J. Immunol. 158, 2065-75 (1997). The mechanism of this inhibition may involve suppression of the induction of the **CIITA** regulatory elements disclosed herein by IFN-.gamma..

DETD STAT1 Activates the Inducibility of the 5' Flanking Region of the **CIITA** Gene in Response to IFN-.gamma.

DETD To investigate the role of STAT1 in activation of IFN-.gamma. inducibility of the 5' flanking sequences of the **CIITA** gene, STAT1 defective U3A cells were transiently transfected with the p6374CIITA.Luc in combination with a STAT1 expression vector plasmid (Improta. . . of the class II MHC gene HLA-DR.alpha., which have been shown to be required for activation of this promoter by **CIITA** in response to IFN-.gamma.. Zhou & Glimcher, Immunity 2, 545-53 (1995); Riley et al., Immunity 2, 533-43 (1995).

L3 ANSWER 39 OF 47 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:880065 CAPLUS

DOCUMENT NUMBER: 135:28808

TITLE: Effects of **CIITA antisense** RNA on the expression of HLA class II molecules

AUTHOR(S): Zhou, Caihong; Lu, Daru; Zhu, Qiquan; Qiu, Xinfang; Xue, Jinglun

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SOURCE: Chinese Science Bulletin (2000), 45(22), 2068-2071 CODEN: CSBUEF; ISSN: 1001-6538

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REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Effects of **CIITA antisense** RNA on the expression of HLA class II molecules

AB To study the effect of the major histocompatibility complex class II (MHC II) transactivator (**CIITA**) **antisense** RNA on the expression of the human leukemia (HLA) class II mols., 5' end cDNA sequence of **CIITA** gene was cloned, and **antisense** RNA expression vector pcDNA-II was constructed. HeLa cells transfected with pcDNA-II and pcDNA3 were induced by IFN-.gamma. for 3 d. The expression of HLA class II mols. on HeLa/pcDNA-II cells was significantly decreased, while it has no effect on the expression of HLA class I mols. This result suggests that the **CIITA antisense** RNA can inhibit the expression of HLA class II mols. in HeLa cells. It also implies a promising approach to generate immune tolerance in graft transplantation.

ST **CIITA antisense** RNA immune tolerance HLA

IT Transcription factors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**CIITA** (class II transactivator); effects of **CIITA antisense** RNA on expression of HLA class II mols.)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HLA, expression of class II mols; effects of **CIITA antisense** RNA on expression of HLA class II mols.)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), class II; effects of **CIITA antisense** RNA on expression of HLA class II mols.)

IT Immune tolerance
(effects of **CIITA antisense** RNA on expression of HLA class II mols.)

IT **Antisense** RNA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of **CIITA antisense** RNA on expression of HLA class II mols.)

IT Genetic vectors
(pcDNA-II; effects of **CIITA antisense** RNA on expression of HLA class II mols.)

L3 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:326045 CAPLUS
DOCUMENT NUMBER: 130:333755
TITLE: Human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators
INVENTOR(S): Glimcher, Laurie H.; Zhou, Hong
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
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WO 9924570	A1	19990520	WO 1998-US22934	19981028
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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US 6410261	B2	20020625		
AU 9912861	A1	19990531	AU 1999-12861	19981028
AU 736150	B2	20010726		
EP 961828	A1	19991208	EP 1998-956308	19981028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001508313	T2	20010626	JP 1999-526487	19981028
US 2002146806	A1	20021010	US 2002-121882	20020412

PRIORITY APPLN. INFO.: US 1997-965272 A 19971106
WO 1998-US22934 W 19981028

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators

AB Isolated nucleic acid mols. encoding a novel protein, CIP104, that interacts with **CIITA**, an MHC class II transcriptional activator, are disclosed. The invention further provides **antisense** nucleic acid mols., recombinant expression vectors contg. a nucleic acid mol. of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals carrying a CIP104 transgene. The invention further provides isolated CIP104 proteins and peptides, CIP104 fusion proteins and anti-CIP104 antibodies. Methods of using the CIP104 compns. of the invention are also disclosed, including methods for detecting CIP104 activity (e.g., CIP104 protein or mRNA) in a biol. sample, methods of modulating CIP104 activity in a cell, and methods for identifying agents that modulate an interaction between CIP104 and **CIITA**. Thus, a yeast two-hybrid assay was used to identify a cDNA encoding a **CIITA**-binding protein, CIP104. Northern blots showed CIP104 mRNA in most tissues examd., but thymus exhibited the highest level of expression. CIP104, in the presence of **CIITA**, activated expression of a reporter gene fused to the DR.alpha. promoter.

ST sequence human **CIITA** interacting protein CIP104 cDNA; immunomodulator screening CIP104 **CIITA** reporter gene

IT Transcription factors
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**CIITA**; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Mouse
(CIP104 gene of; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT RNA formation factors
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(CIP104; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Promoter (genetic element)
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(DR.alpha., reporter gene fused to; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HLA-DR, promoter of gene for, reporter gene fused to; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MHC (major histocompatibility complex), class II, promoter of gene for, reporter gene fused to; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Reporter gene
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(MHC II gene promoter fused to; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Immunomodulators
(human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Antibodies
Probes (nucleic acid)
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Antibodies
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(monoclonal; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Molecular cloning

(of CIP104 gene; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT Animal
(transgenic, CIP104 gene-expressing; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT 224428-33-5
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(amino acid sequence; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

IT 224428-32-4
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; human **CIITA**-interacting protein CIP104 and cDNA and methods of screening for immunomodulators)

L3 ANSWER 41 OF 47 USPATFULL

ACCESSION NUMBER: 1999:63235 USPATFULL

TITLE: Transcription factor regulating MHC expression CDNA and genomic clones encoding same and retroviral expression constructs thereof

INVENTOR(S): Ono, Santa Jeremy, Baltimore, MD, United States
Strominger, Jack L., Lexington, MA, United States

PATENT ASSIGNEE(S): The Johns Hopkins University, Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5908762		19990601
APPLICATION INFO.:	US 1997-828584		19970331 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-327832, filed on 21 Oct 1994		

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Schwartzman, Robert
LEGAL REPRESENTATIVE: Banner & Witcoff, Ltd.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 26 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 2266
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Recently, a novel factor (**CIITA**) required for both constitutive and interferon.gamma. mediated expression of all of the class II MHC genes has been isolated by. . . al., 1994, Science, 265:106). This factor does not appear to interact directly with the class II MHC proximal promoter, but **CIITA** transactivation is mediated by the proximal promoter (presumably via protein-protein interactions between **CIITA** and other class II promoter binding proteins).

SUMM . . . aIr-1 and sIr-1 that encode either activator(s) or silencer(s) of class II MHC gene expression, respectively. The newly isolated cDNA (**CIITA**, located on human chromosome 16) appears to encode aIr-1 (Steimle, et al., 1993; Steimle, et al., 1994).

DRWD . . . reporter construct DRA300CAT and increasing amounts of the LNCX expression vectors containing the NF-X1 cDNA in either the sense or **antisense** orientations. C) Histograms showing CAT activity in Raji cells after cotransfection with DRA300CAT and expression vectors containing the previously described. . .

DETD . . . promoter reporter construct DRA300CAT and increasing amounts of expression vectors containing the suspected NF-X1 cDNA in either the sense or **antisense** orientations are compared to those for the class II inducible cell line HeLa. Wild-type NF-X1 has been found to encode. . .

DETD . . . labeled HELA+INF were extracted from HeLa cells incubated for

24 hours with 250 U/ml interferon-g. For RNase protection analysis an **antisense** probe for the human gamma-actin gene was synthesized by linearizing the plasmid SP6-gamma-actin (Zinn, et al., 1983, Cell, 34:865) with. . . and 32P CTP (800 Ci/mmol; DuPont/NEN). 3.2 kilobases of the NF-X1 cDNA was subcloned into pbluescript to generate pBSClone-16. The **antisense** probe for NF-X1 was prepared by first linearizing the pBSClone-16 plasmid with AatII and transcribed using T7 RNA polymerase. 25. . .

DETD . . . reporter construct DRA300CAT and increasing amounts of the LNCX expression vectors containing the NF-X1 cDNA in either the sense or **antisense** orientations are shown in FIG. 5B. CAT activities are normalize to a cotransfected HGH expression vector as described (Ono, et. . .

L3 ANSWER 42 OF 47 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000069222 MEDLINE
DOCUMENT NUMBER: 20069222 PubMed ID: 10602887
TITLE: Cancer immunotherapy by **antisense** suppression of Ii protein in MHC-class-II-positive tumor cells.
AUTHOR: Qiu G; Goodchild J; Humphreys R E; Xu M
CORPORATE SOURCE: Antigen Express Inc., One Innovation Drive, Worcester, MA 01605, USA.
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1999 Dec) 48 (9) 499-506.
Journal code: 8605732. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000111

TI Cancer immunotherapy by **antisense** suppression of Ii protein in MHC-class-II-positive tumor cells.

AB . . . the range of cancer-related epitopes presented to CD4+ helper T cells. Effective suppression of Ii protein was achieved with an **antisense**, phosphorothioate oligonucleotide, which was selected on the basis of (1) the RNase H activation assay, (2) an assay for Ii. . . The SaI murine sarcoma, which is MHC-class-I+ and MHC-class-II-, Ii-protein-, upon transfection with genes for either interferon gamma or the **MHC class II transactivator**, came to express MHC class II molecules and Ii protein. In each line of transfected tumor cells, the **antisense** oligonucleotide profoundly suppressed Ii protein in 35%-55% cells, without affecting expression of MHC class II molecules. Inoculation of mice with. . .

CT . . .

GE, genetics
*Histocompatibility Antigens Class II: IM, immunology
*Immunotherapy
Interferon Type II: GE, genetics
Mice
Mice, Inbred A
Neoplasm Transplantation
***Oligodeoxyribonucleotides, Antisense: TU, therapeutic use**
Sarcoma, Experimental: GE, genetics
Sarcoma, Experimental: IM, immunology
Sarcoma, Experimental: PA, pathology
*Sarcoma, Experimental: PC, prevention. . .

CN 0 (Antigens, Differentiation, B-Lymphocyte); 0 (Antigens, Neoplasm); 0 (Cancer Vaccines); 0 (Histocompatibility Antigens Class II); 0 (Oligodeoxyribonucleotides, **Antisense**); 0 (Thionucleotides); 0 (invariant chain)

L3 ANSWER 43 OF 47 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:239287 CAPLUS
DOCUMENT NUMBER: 128:281721
TITLE: Mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression
INVENTOR(S): Fabre, John William; Gustafsson, Kenth Tomas; Yun, Sheng
PATENT ASSIGNEE(S): Institute of Child Health, UK; Fabre, John William; Gustafsson, Kenth Tomas; Yun, Sheng
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815626	A2	19980416	WO 1997-GB2751	19971008
WO 9815626	A3	20000817		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

ZA 9709030	A	19980423	ZA 1997-9030	19971008
AU 9745675	A1	19980505	AU 1997-45675	19971008

PRIORITY APPLN. INFO.:

GB 1996-20940	A	19961008
GB 1997-5911	A	19970321
WO 1997-GB2751	W	19971008

TI Mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression

AB A polypeptide is provided that comprises the amino acid sequence of a class II trans activator (**CIITA**) protein from the N-terminus of which amino acid residues are missing such that the resulting polypeptide reduces the expression of MHC class II antigens. Deletion of the first 151 amino acids from the N-terminus of human **CIITA** results in strong suppression of MHC class II antigen synthesis both in cells that express the antigens constitutively and in cells that are susceptible to lymphokine induction of expression. The deletion polypeptide was expressed from a mutated cDNA which incorporated the first 6 codons (i.e., the start codon and the 5 codons corresponding to amino acids 2-6 of native human **CIITA**) at the 5'-end of the construct followed by a codon for isoleucine. The remainder of the construct comprises the codons for amino acid 152 to the end of the sequence. The mutant **CIITA** is useful in the treatment of autoimmune disease and in the prodn. of transgenic donor animals for xenografts and in the treatment of autoimmune diseases. A hammerhead **ribozymes** targeting bases 1159-1161 of human **CIITA** are also useful, as are nucleic acids encoding the polypeptide and the **ribozyme**.

ST transcription factor **CIITA** mutant immunosuppression; **ribozyme** transcription factor **CIITA** mRNA immunosuppression

IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**CIITA** (class II transactivator); mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(HLA-DR; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), class II; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SLA (swine leukocyte antigen), class II; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Blood vessel
(endothelium, promoter of ICAM-2 gene specific for; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT DNA sequences
(for mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT **Ribozymes**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hammerhead; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Gene therapy
Immunosuppressants
Immunosuppression
Molecular cloning
Swine
(mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Protein sequences
(of mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Animal
Animal cell
Animal tissue
Organ, animal
(transgenic; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Autoimmune disease
(treatment of; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(vascular endothelial cell-specific; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT Transplant and Transplantation
(xenotransplant; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT 152988-72-2P 205887-89-4P
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

IT 151580-64-2, GenBank X74301 205887-88-3

RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; mutant N-terminal truncated **CIITA** transactivator and its uses for immunosuppression)

L3 ANSWER 44 OF 47 USPATFULL

ACCESSION NUMBER:	1998:147545 USPATFULL
TITLE:	Transcription factor regulating MHC expression, CDNA and genomic clones encoding same and retroviral expression constructs thereof
INVENTOR(S):	Ono, Santa Jeremy, Baltimore, MD, United States Strominger, Jack L., Lexington, MA, United States
PATENT ASSIGNEE(S):	The Johns Hopkins University, Baltimore, MD, United States (U.S. corporation) The President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5840832		19981124	
APPLICATION INFO.:	US 1994-327832		19941021	(8)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Elliott, George C.			
ASSISTANT EXAMINER:	Wai, Thanda			
LEGAL REPRESENTATIVE:	Banner & Witcoff, Ltd.			
NUMBER OF CLAIMS:	5			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	25 Drawing Figure(s); 19 Drawing Page(s)			
LINE COUNT:	2119			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Recently, a novel factor (**CIITA**) required for both constitutive and interferon-.gamma. mediated expression of all of the class II MHC genes has been isolated by. . . al., 1994, Science, 265:106). This factor does not appear to interact directly with the class II MHC proximal promoter, but **CIITA** transactivation is mediated by the proximal promoter (presumably via protein-protein interactions between **CIITA** and other class II promoter binding proteins).

SUMM . . . aIr-1 and sIr-1 that encode either activator(s) or silencer(s) of class II MHC gene expression, respectively. The newly isolated cDNA (**CIITA**, located on human chromosome 16) appears to encode aIr-1 (Steimle, et al., 1993; Steimle, et al., 1994).

DRWD . . . reporter construct DRA300CAT and increasing amounts of the LNCX expression vectors containing the NF-X1 cDNA in either the sense or **antisense** orientations. C) Histograms showing CAT activity in Raji cells after cotransfection with DRA300CAT and expression vectors containing the previously described. . .

DETD . . . promoter reporter construct DRA300CAT and increasing amounts of expression vectors containing the suspected NF-X1 cDNA in either the sense or **antisense** orientations are compared to those for the class II inducible cell line HeLa. Wild-type NF-X1 has been found to encode. . .

DETD . . . labeled HELA+INF were extracted from HeLa cells incubated for 24 hours with 250 U/ml interferon-g. For RNase protection analysis an **antisense** probe for the human gamma-actin gene was synthesized by linearizing the plasmid SP6-gamma-actin (Zinn, et al., 1983, Cell, 34:865) with. . . and 32P CTP (800 Ci/mmol; DuPont/NEN). 3.2 kilobases of the NF-X1 cDNA was subcloned into pBluescript to generate pBSClone-16. The **antisense** probe for NF-X1 was prepared by first linearizing the pBSClone-16 plasmid with AatII and transcribed using T7 RNA polymerase. 25. . .

DETD . . . reporter construct DRA300CAT and increasing amounts of the LNCX expression vectors containing the NF-X1 cDNA in either the sense or **antisense** orientations are shown in FIG. 5B. CAT activities are

normalized to a cotransfected HGH expression vector as described (Ono, et. . .

L3 ANSWER 45 OF 47 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 96322744 MEDLINE
DOCUMENT NUMBER: 96322744 PubMed ID: 8759739
TITLE: Stat1 alpha expression is involved in IFN-gamma induction of the class II transactivator and class II MHC genes.
AUTHOR: Lee Y J; Benveniste E N
CORPORATE SOURCE: Department of Cell Biology, University of Alabama at Birmingham 35294, USA.
CONTRACT NUMBER: AM-20614 (NIADDK)
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 Aug 15) 157 (4) 1559-68. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960924
Last Updated on STN: 19970203
Entered Medline: 19960917

AB . . . Jak1 and Jak2 and of Stat1 alpha. In addition, IFN-gamma enhances expression of Stat1 alpha mRNA and protein. We utilized **antisense** oligonucleotides against Stat1 alpha to determine directly whether IFN-gamma-induced activation and/or enhancement of Stat1 alpha is involved in class II expression. **Antisense** oligonucleotides complementary to Stat1 alpha mRNA were introduced in CH235-MG astroglioma cells by transient transfection; such treatment inhibited both constitutive. . . and IFN-gamma-enhanced expression of Stat1 alpha. IFN-gamma-induced class II MHC expression was also inhibited in cells exposed to Stat1 alpha **antisense** oligonucleotides. The fact that the class II promoter does not contain IFN-gamma-activated sequences for binding Stat1 alpha suggests that Stat1. . . activate another protein that is directly involved in class II expression. A likely candidate is the class II MHC transactivator (**CIITA**). IFN-gamma induction of **CIITA** mRNA was also inhibited in cells treated with **antisense** oligonucleotides against Stat1 alpha. These findings demonstrate that Stat1 alpha is involved in IFN-gamma induction of **CIITA** expression, resulting in class II MHC expression.

CT . . .
Sequence Data
Neoplasm Proteins: BI, biosynthesis
Neoplasm Proteins: GE, genetics
Nerve Tissue Proteins: BI, biosynthesis
Nerve Tissue Proteins: GE, genetics
Oligonucleotides, Antisense: PD, pharmacology
Promoter Regions (Genetics)
RNA, Messenger: AI, antagonists & inhibitors
RNA, Messenger: GE, genetics
*Signal Transduction: DE, . . .

CN 0 (**CIITA** protein); 0 (DNA-Binding Proteins); 0 (Neoplasm Proteins); 0 (Nerve Tissue Proteins); 0 (Oligonucleotides, **Antisense**); 0 (RNA, Messenger); 0 (Trans-Activators); 0 (gamma-activated factor, 91-kD)

L3 ANSWER 46 OF 47 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:712099 CAPLUS
DOCUMENT NUMBER: 123:76446
TITLE: A gene for a transactivator (**CIITA**) of MHC class II antigen gene expression and uses of the transactivator gene
INVENTOR(S): Mach, Bernard Francois
PATENT ASSIGNEE(S): Switz.

SOURCE: Eur. Pat. Appl., 32 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 648836	A1	19950419	EP 1994-113378	19940826
EP 648836	B1	20020109		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 211763	E	20020115	AT 1994-113378	19940826
ES 2170082	T3	20020801	ES 1994-113378	19940826
US 5994082	A	19991130	US 1995-519547	19950825
JP 08224087	A2	19960903	JP 1995-219341	19950828
US 2002155542	A1	20021024	US 2002-104595	20020320

PRIORITY APPLN. INFO.:
EP 1993-113665 A 19930826
EP 1994-113378 A 19940826
US 1995-519547 A1 19950825
US 1999-413786 B1 19991007

TI A gene for a transactivator (**CIITA**) of MHC class II antigen gene expression and uses of the transactivator gene

IT Ribonucleic acid formation factors
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(**CIITA**; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

IT Gene, animal
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(cDNA; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

IT Protein sequences
(of **CIITA** transactivator of human; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

IT Plasmid and Episome
(pDVP10-1, cDNA for **CIITA** transactivator of class II MHC antigen gene expression on; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

IT Vaccines
(stimulation of class II MHC antigen gene expression in vaccination; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

IT Neoplasm inhibitors
(stimulation of class II MHC antigen gene expression; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

IT **Ribozymes**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to transcript for transactivator of class II MHC antigen gene expression; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

IT Animal
(transgenic, as organ donors, minimization of class II MHC antigen gene expression in; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(MHC (major histocompatibility antigen complex), class II, gene for transactivator (**CIITA**) of MHC class II antigen gene

expression and uses of transactivator gene)
IT Ribonucleic acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antisense**, to transactivator of class II MHC antigen gene expression; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)
IT Deoxyribonucleic acid sequences
(complementary, for **CIITA** transactivator of human; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)
IT Deoxyribonucleic acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(complementary, **antisense**, to transactivator of class II MHC antigen gene expression; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)
IT Immunity
(disorder, treatment of, alteration of class II MHC antigen gene expression in; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)
IT Therapeutics
(geno-, of abnormal class II MHC antigen gene expression; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)
IT Transplant and Transplantation
(xeno-, minimization of class II MHC antigen gene expression in donor animal; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)
IT 152988-72-2
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)
IT 151580-64-2
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; gene for transactivator (**CIITA**) of MHC class II antigen gene expression and uses of transactivator gene)

L3 ANSWER 47 OF 47 MEDLINE
ACCESSION NUMBER: 95323672 MEDLINE
DOCUMENT NUMBER: 95323672 PubMed ID: 7600294
TITLE: Molecular analysis of G1B and G3A IFN gamma mutants reveals that defects in **CIITA** or RFX result in defective class II MHC and Ii gene induction.
AUTHOR: Chin K C; Mao C; Skinner C; Riley J L; Wright K L; Moreno C S; Stark G R; Boss J M; Ting J P
CORPORATE SOURCE: Department of Biochemistry and Biophysics, University of North Carolina, Chapel Hill 27599-7260, USA.
CONTRACT NUMBER: AI29564 (NIAID)
AI34000 (NIAID)
CA37172 (NCI)
+
SOURCE: IMMUNITY, (1994 Nov) 1 (8) 687-97.
Journal code: 9432918. ISSN: 1074-7613.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950822
Last Updated on STN: 19950822
Entered Medline: 19950810
TI Molecular analysis of G1B and G3A IFN gamma mutants reveals that defects

in **CIITA** or RFX result in defective class II MHC and Ii gene induction.

AB . . . the DNA-binding proteins that interact with these elements are regulated by IFN gamma. Recently, a gene coding for a transactivator (**CIITA**) of class II MHC genes that complements a HLA-DR-negative immunodeficiency has been isolated. Using one IFN gamma mutant cell line (G3A) that is selectively defective in HLA-DR and Ii induction, four lines of evidence are presented to show that **CIITA** mediates the IFN gamma induction of HLA-DR and Ii genes. Analysis of another mutant line, G1B, indicates that the lack. . .

CT . . .

BI, biosynthesis
*Histocompatibility Antigens Class II: GE, genetics
*Interferon Type II: PD, pharmacology
Molecular Sequence Data
Mutation
Promoter Regions (Genetics)
RNA, Antisense: PD, pharmacology
Recombinant Fusion Proteins: BI, biosynthesis
Regulatory Sequences, Nucleic Acid
Time Factors
*Trans-Activators: PH, physiology
Transfection

CN 0 (Antigens, Neoplasm); 0 (**CIITA** protein); 0 (HLA-DR Antigens); 0 (HLA-DRA); 0 (Histocompatibility Antigens Class II); 0 (RNA, **Antisense**); 0 (Recombinant Fusion Proteins); 0 (Trans-Activators); 0 (invariant chain)

GEN **CIITA**; DRA; Ii

=>

=>
Executing the logoff script...

=> LOG H

COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	210.87	211.08

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-9.77	-9.77

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 11:11:28 ON 04 JUN 2003